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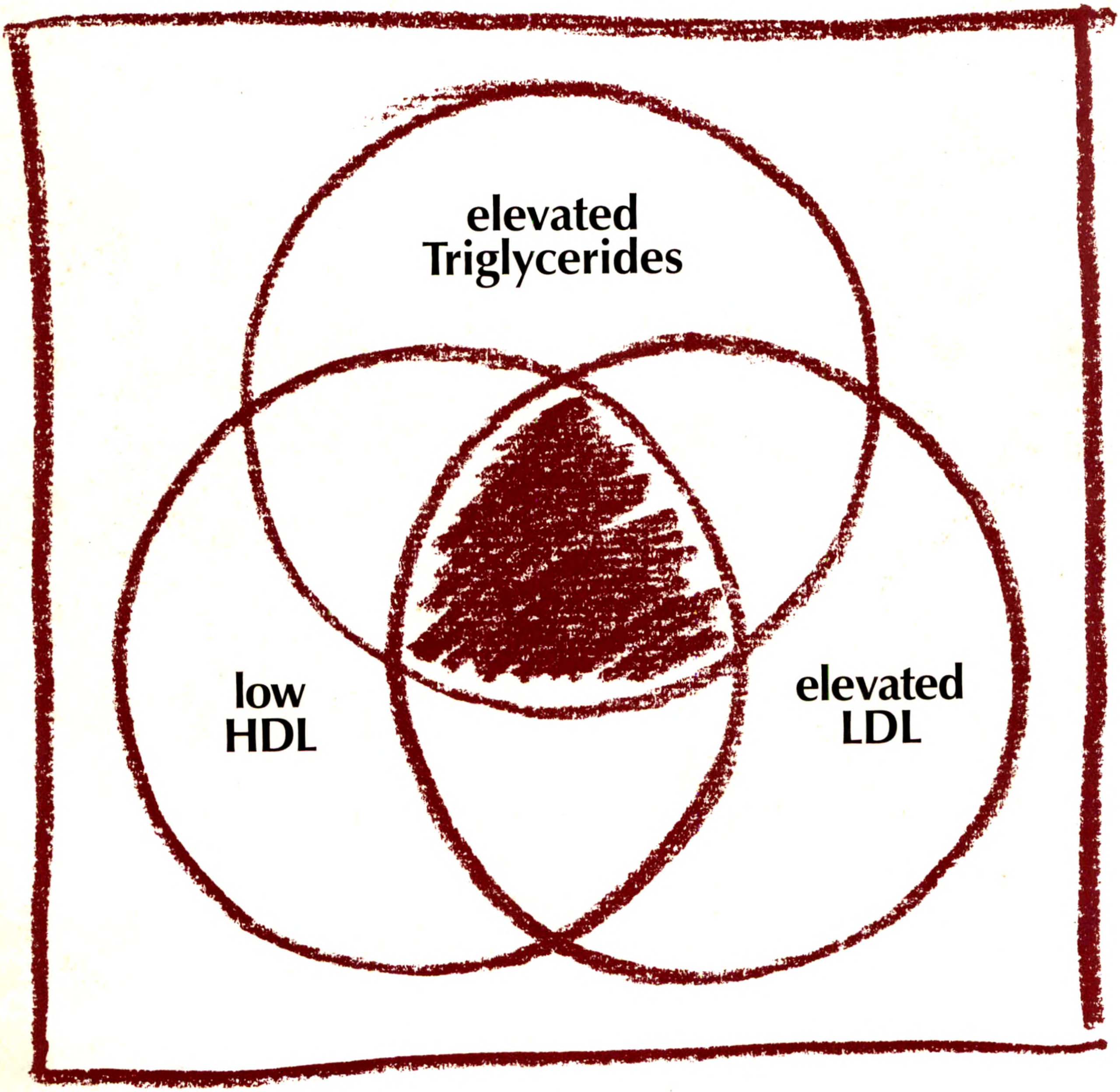
Reduce the risk of developing CHD in patients with the triad of risk...



As an adjunct to diet, after an inadequate response to exercise, dietary therapy, weight loss and trial of other pharmacologic agents (such as bile acid sequestrants and nicotinic acid)

LOPID®

(gemfibrozil) 600-mg Tablets BID

REDUCES THE RISK OF DEVELOPING CHD
IN PATIENTS WITH THE TRIAD OF RISK

LOPID is indicated as adjunctive therapy to diet for reducing the risk of developing coronary heart disease **only** in Type IIb patients:

- Without history of or symptoms of existing coronary heart disease
- Who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol)

and

- Who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides

In addition:

- The potential benefit of gemfibrozil in treating Type IIa patients with elevations of LDL-cholesterol only is not likely to outweigh the risks
- LOPID is not indicated for the treatment of patients with low HDL-cholesterol as their only lipid abnormality

LOPID is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil

LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis

Caution should be exercised when anticoagulants are given in conjunction with LOPID

Please see last page of this advertisement for brief summary of prescribing information.

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LOPID®

(gemfibrozil) 600-mg Tablets BID

Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. Preexisting gallbladder disease (see WARNINGS).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo groups at year-5 or at year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to Lopid and 9 in the group originally randomized to placebo ($p = 0.22$). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to Lopid and 18 (0.9%) in the group originally randomized to placebo ($p = 0.11$). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. See CLINICAL PHARMACOLOGY section in full prescribing information which includes the following: The secondary prevention component of the Helskinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88-2.48, $p=0.14$). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the Lopid group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94-5.05, $p=0.06$). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has shown benefit only in selected dyslipidemic patients *without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **HMG-CoA reductase inhibitors:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin (or other HMG-CoA reductase inhibitors) and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats at 0.2 and 2 times the human dose (based on surface area, mg/meter^2). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p = 0.1$). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign, and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 1 times the human dose (based on surface area). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 0.6 and 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C** – Lopid has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area) but no developmental toxicity or teratogenicity among offspring of either species. There are no adequate and well-controlled studies in pregnant women. Lopid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of Lopid to female rats at 0.6 and 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and, at the high dose, an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of Lopid to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of Lopid to female rabbits during organogenesis caused a dose-related decrease in litter size and at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers** – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Lopid in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Kidney Function** – There have been reports of worsening renal insufficiency upon the addition of Lopid therapy in individuals with baseline plasma creatinine > 2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of Lopid.

10. **Use in Children** – Safety and efficacy in children and adolescents have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N=2046)	PLACEBO (N=2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1
Adverse events reported by more than 1% of subjects, but without a significant difference between groups:		
Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% vs. 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs. 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility, renal dysfunction; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSAGE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20	Bottles of 60
N 0071-0737-30	Bottles of 500
N 0071-0737-40	Unit dose packages of 100 (10 strips of 10 tablets each)

Parcode® No. 737

Storage: Store below 30° C (86° F).

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4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36-39.

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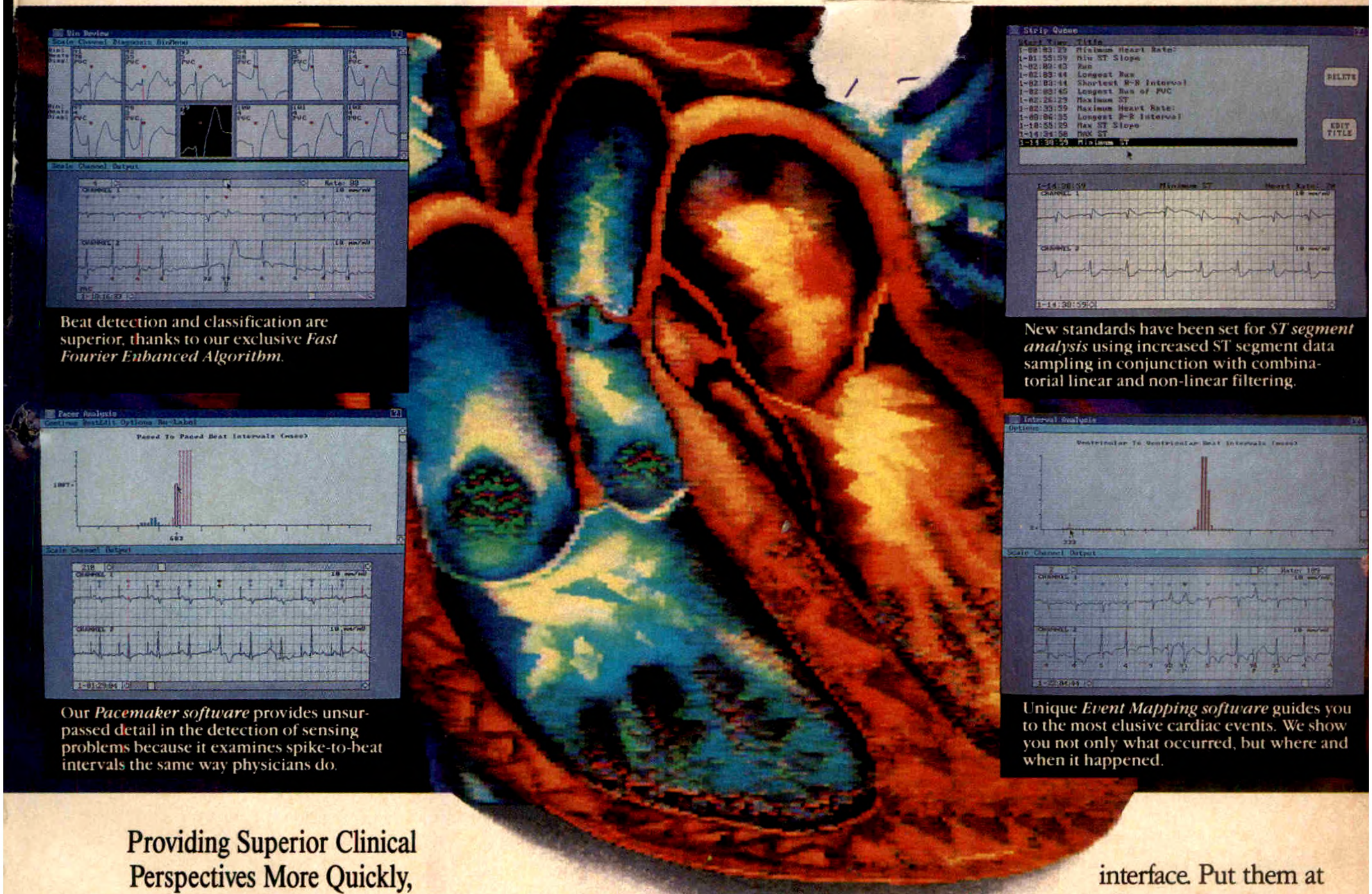

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CORONARY ARTERY DISEASE

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Clinical, Hemodynamic, Electrocardiographic and Mechanical Events During Nonocclusive, Coronary Atherectomy and Comparison with Balloon Angioplasty

Gregory S. Pavlides, Andrew M. Hauser, Cindy L. Grines, Patricia I. Dudlets, and William W. O'Neill

To assess periprocedural clinical events and myocardial function, 17 patients undergoing Rotablator and 18 transluminal extraction catheter (TEC) atherectomy were studied. Subsequent adjunctive balloon angioplasty was performed in 16 of 17 patients undergoing Rotablator and 14 of 18 patients undergoing TEC atherectomy. Chest pain occurred more frequently during balloon inflation than during either atherectomy, whereas electrocardiographic changes were equally observed. Hemodynamic parameters and global left ventricular function remained unchanged during atherectomy. Transient second- or third-degree atrioventricular block was observed during Rotablator atherectomy in 6 patients. Regional myocardial infarction was not affected during Rotablator atherectomy, but transiently deteriorated slightly during TEC atherectomy (score from 0.3 ± to 1.0 ± 0.7, $p < 0.005$) and more significantly during balloon inflation (score to 2.0 ± 0.6, $p < 0.001$). These data suggest that clinical evidence of ischemia occurs less frequently during Rotablator or TEC atherectomy than during balloon angioplasty, which may be an important advantage in certain patients with coronary artery disease.

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Effects of Exercise Test Results on Physician Perceptions of Coronary Artery Disease Probability Using a Threshold Analysis

David A. Wilson, Robert C. Detrano, Kenneth A. Narahara, Bruce H. Brundage, Demetrios Georgiou, William J. French, Leonard E. Ginzton, Shelley M. Shapiro, Marco Bobbio, and Adrian Shandling

The incremental value of exercise testing results in establishing the diagnosis of coronary artery disease (CAD) when combined with history and clinical data was evaluated. Clinical data from 312 patients who had coronary angiography were presented to 8 cardiologists with and without exercise test results. The cardiologists then provided probability assessments for the presence of any CAD and 3-vessel or left main CAD, and were asked whether angiography was indicated. Probability thresholds for any CAD and 3-vessel/left main CAD at which each cardiologist believed

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angiography was indicated were determined. Fifteen additional patients with 3-vessel or left main CAD were above a threshold after the exercise test. Thus, exercise test results assessed by clinical cardiologists improve the prediction of CAD in patients with both high and low pretest probabilities of 3-vessel or left main CAD.

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Atherosclerosis of the Aorta and Coronary Arteries and Cardiovascular Risk Factors in Persons Aged 6 to 30 Years and Studied at Necropsy (The Bogalusa Heart Study)

Gerald S. Berenson, Wendy A. Wattigney, Richard E. Tracy, William P. Newman III, Sathanur R. Srinivasan, Larry S. Webber, Edward R. Dalferes, Jr., and Jack P. Strong

The relation of atherosclerotic lesions to antemortem cardiovascular risk factors was studied in young persons. The intimal surface involved with aorta fatty streaks was extensive and greater in blacks than in whites. Coronary artery fatty streaks were more extensive in male than in female subjects. The relation of fatty streaks to fibrous plaques was greater in the coronary vessels. For white male subjects, aorta fatty streaks were strongly related to antemortem levels of total cholesterol, low-density lipoprotein cholesterol and ponderal index. Coronary artery fatty streaks were significantly associated with serum triglycerides, very low density lipoprotein cholesterol, systolic and diastolic blood pressure and ponderal index. There was a strong relation of total cholesterol and low-density lipoprotein cholesterol to aorta fatty streaks in black male subjects, but a significant association with coronary lesions was lacking. These observations show direction and need for emphasizing preventive cardiology in early life.

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Efficacy of Enhanced External Counterpulsation in the Treatment of Angina Pectoris

William E. Lawson, John C.K. Hui, Harry S. Soroff, Zhen Sheng Zheng, David S. Kayden, Dawn Sasvary, Harold Atkins, and Peter F. Cohn

Eighteen patients with angina were treated with an improved system of enhanced external counterpulsation (EECP), using additional thigh balloons and sequenced balloon inflation (1 hour daily for 36 hours). A baseline maximal thallium-201 stress test was performed and repeated for the same exercise duration after EECP treatment. A maximal stress test after EECP was also performed. All patients had improvement in anginal symptoms, with reduced usage of antianginal medications. Thallium stress testing after EECP showed complete resolution of ischemic defects in 12 patients (67%), reduction in ischemic area in 2 (11%), and no change in 4 (22%) ($p < 0.01$). The exercise duration of maximal stress testing after EECP showed significant improvement when compared with before EECP (9.72 ± 0.77 vs 8.14 ± 0.71 minutes; $p < 0.005$). Although the double product did not change significantly (22,816 ± 1,653 vs 22,062 ± 1,664 mm Hg · beats/min), subgroup analysis of 14 patients with improved thallium scans showed significant improvement in both exercise duration (8.58 ± 0.66 to 10.44 ± 0.59 minutes; $p < 0.001$) and double

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product (21,827 ± 2,044 to 24,842 ± 1,707 mm Hg · beats/min; $p < 0.01$). EECP appears to be a safe and effective therapy for selected patients with angina.

863

Assessment of Left Ventricular Function in Kawasaki Disease by Dipyridamole-Loading Cineventriculography

Takashi Kosuda and Katsuhiko Sone

Dipyridamole-loading cineventriculography was performed to evaluate left ventricular (LV) function in 76 patients with Kawasaki disease. Global ejection fraction of the left ventricle increased in patients with normal findings on the coronary angiogram, but there was no significant change in patients with dilated coronary lesions >4 mm and with stenotic coronary lesions. In 70% of patients with stenotic coronary lesions, abnormal LV wall motion after administration of dipyridamole was detected. There were several cases of abnormal LV wall motion in patients with dilated coronary lesions only, and the abnormality was detected by dipyridamole infusion.

PREVENTIVE CARDIOLOGY

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Effect of Fat-Modified and Fruit- and Vegetable-Enriched Diets on Blood Lipids in the Indian Diet Heart Study

Ram B. Singh, Shanti S. Rastogi, Mohammad A. Niaz, Saraswati Ghosh, Reema Singh, and Shobha Gupta

The Indian Diet Heart Study was designed to test the efficacy of the administration of fruits and vegetables for 12 weeks as an adjunct to a prudent diet in decreasing blood lipids in 310 (intervention; group A) and 311 (control; group B) patients with risk factors of coronary artery disease (CAD) in a parallel, single-blind fashion. Fruits and vegetables decreased the total and low-density lipoprotein cholesterol levels by 6.5 and 7.3%, respectively, in group A, whereas the levels were unchanged in group B. The high-density lipoprotein cholesterol levels that decreased during the diet stabilization period in all patients, increased by 5.6% in group A after 12 weeks. Serum triglycerides also decreased (7%) more in group A than B. Fasting blood glucose decreased by 6.9% in group A and by 2.6% in group B. The combined effect of a fat-modified diet plus fruits and vegetables was greater than these changes. Because fruits are tasty food and easily available at reasonable cost in our marketing and buying capacity, compliance was excellent. It is possible that fruits and vegetables may be a safe adjunct to a prudent diet in free-living subjects with risk factors of CAD for the modulation of blood lipoproteins and for the prevention of CAD.

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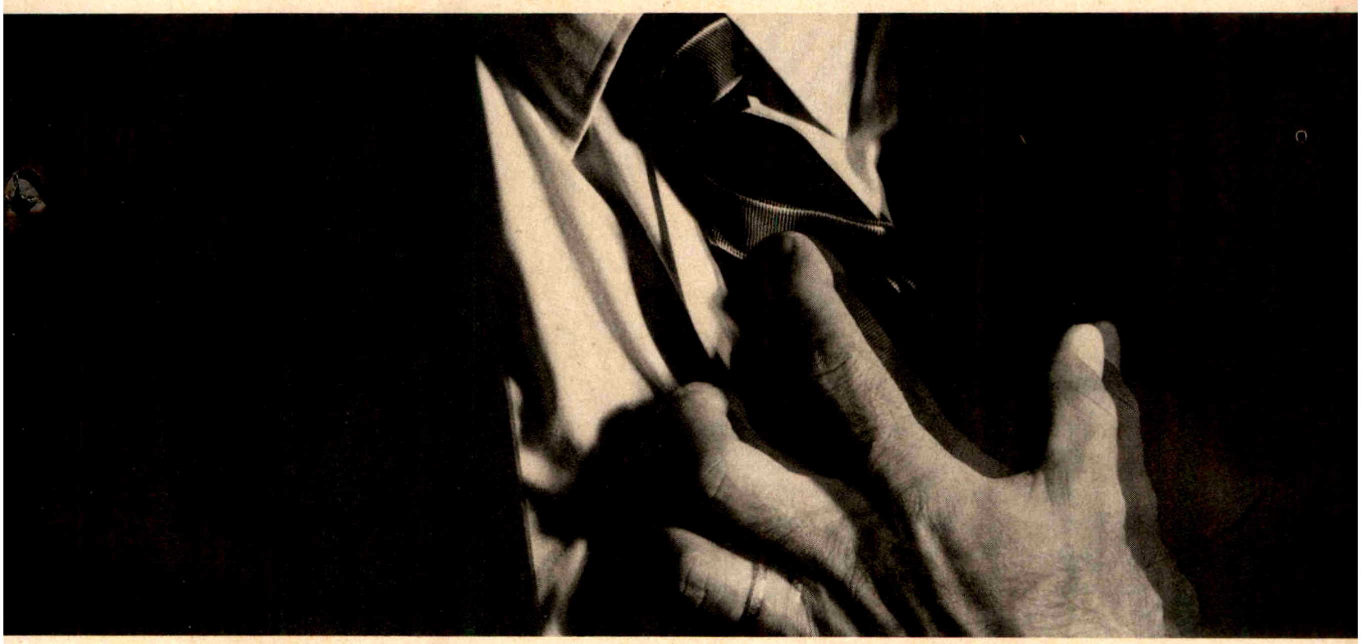
SOME PEOPLE TAKE DRUG ABUSE TO HEART.



Most cocaine users are so dedicated to the drug that what it does to their hearts never enters their minds. They don't realize that every time they use cocaine, they put themselves at risk for such potentially fatal cardiovascular complications as hypertensive crisis…myocarditis…myocardial infarction…ventricular tachycardia…ventricular fibrillation…even cardiac arrest.

Chances are, at least some of these people are your patients. And many of them may feel more comfortable telling a nurse what they can't—or won't—tell a doctor. That's why your role becomes critical in helping suspected drug abusers understand what illegal drug use does to their bodies.

As key members of the health care team, nurses *can* make a difference in helping to curb drug abuse, and in preventing some of its deadliest consequences. The next time you suspect a patient may be using cocaine—or *any* illegal substance—have a heart-to-heart talk about the damage these drugs can do.

A short talk can go a long way.

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Incidence, Pathophysiology and Prognosis of Exercise-Induced Sustained Ventricular Tachycardia Associated with Healed Myocardial Infarction

Gilles E. O'Hara, Pedro Brugada, Luz-Maria Rodriguez, Mitermayer Brito, Luis Mont, Andre Waleffe, Henri Kulbertus, and Hein J. J. Wellens

Of 150 consecutive patients with sustained monomorphic ventricular tachycardia (VT) (n = 116) or fibrillation (n = 34) late after myocardial infarction, 17 patients had reproduction of their sustained monomorphic VT during exercise testing. Data from these patients (group I) were compared with data from patients without exercise-induced VT (group II). No statistical difference was found between groups I and II with relation to age, sex, left ventricular ejection fraction, inducibility during programmed stimulation and total mortality during follow-up. In group I only 1 patient (6%) developed ST depression during exercise compared with 47 patients (35%) in group II ($p < 0.01$). After a 34-month mean follow-up, 6 patients in group I (35%) and 18 patients in group II (13%) died suddenly ($p = 0.02$). It is concluded that electrocardiographic findings do not support ischemia as a triggering mechanism of exercise-induced sustained monomorphic VT. Patients with exercise-induced sustained monomorphic VT have a high incidence of sudden death.

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Clinical and Electrophysiologic Effects of Magnesium Sulfate on Paroxysmal Supraventricular Tachycardia and Comparison with Adenosine Triphosphate

Sami Viskin, Bernard Belhassen, David Sheps, and Shlomo Laniado

Intravenous magnesium sulfate (2 to 4 g) was significantly less effective than adenosine triphosphate (ATP) (10 to 20 mg) for terminating paroxysmal atrioventricular (AV) supraventricular tachycardia. Arrhythmia termination with ATP was due to anterograde AV nodal blockade in 13 of 14 patients, whereas arrhythmia termination by magnesium, observed in 6 of 15 patients was due to retrograde block over an accessory pathway (3 patients), AV nodal conduction block (2 patients) and premature ventricular complexes (1 patient). During induced tachycardias, only AH intervals were prolonged by ATP, whereas magnesium prolonged both AH and QRS intervals. Short-lasting side effects (chest pain, flushing, nausea) occurred after both drugs were administered but were more severe after magnesium.

886

An Anatomically Guided Approach to Atrioventricular Node Slow Pathway Ablation

Mark Wathen, Andrea Natale, Kevin Wolfe, Raymond Yee, David Newman, and George Klein

Radiofrequency ablation of the "slow" pathway of the atrioventricular (AV) node reentrant circuit may be guided by electrophysiologic ("slow

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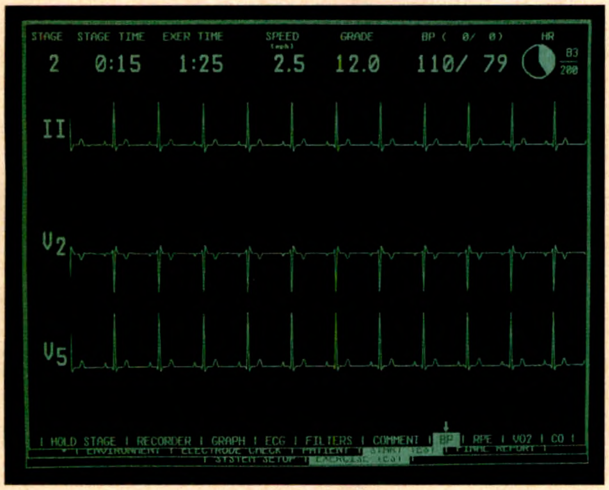
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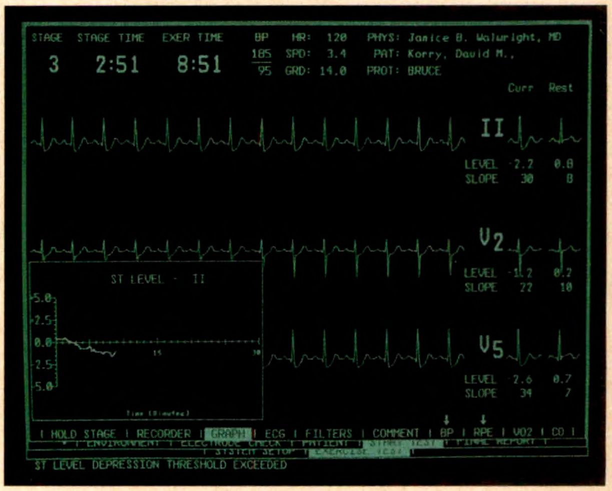
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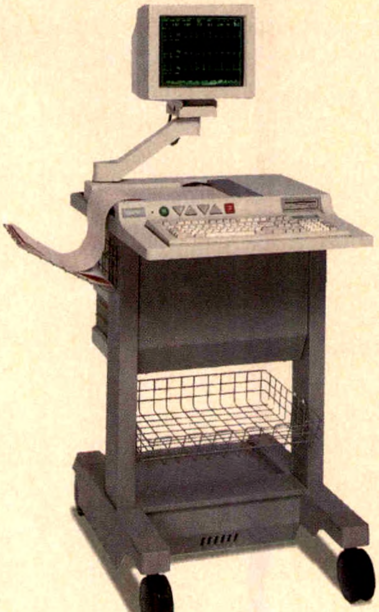

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pathway potential") or anatomic landmarks. We describe our experience with a systematic, anatomically guided approach in 25 patients with typical AV node reentry. The slow pathway is assumed to be the posterior input to the AV node, approaching the nodal region in the corridor between the tricuspid annulus and the orifice of the coronary sinus. A series of radiofrequency lesions are given to interrupt this corridor at its entrance to Koch's triangle. If this is unsuccessful, the series of lesions are repeated progressively at higher levels approaching the AV node. The major end point is elimination of the slow pathway as determined by extrastimulus testing. A mean of 1.2 ± 0.2 ablative sessions achieved clinical success in 24 of 25 patients (96%) at a follow-up of 8.6 ± 2.2 months. This approach provides a systematic, expedient technique to eliminate slow pathway conduction based on anatomic landmarks.

CONGESTIVE HEART FAILURE

890

Renal Response to Indomethacin in Congestive Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

Stephen S. Gottlieb, Shawn Robinson, Catherine M. Krichten, and Michael L. Fisher

Twenty-five patients with severe congestive heart failure were studied to assess the renal effects of indomethacin and the relation between indomethacin-induced changes in glomerular filtration rate and renal plasma flow. Three days after baseline measurement of glomerular filtration rate and renal plasma flow, 75 mg of sustained-release indomethacin were administered, and repeat renal function tests were performed. Mean glomerular filtration rate decreased from 40 ± 21 to 32 ± 16 ml/min/1.73 m^2 ($p < 0.05$), and mean renal plasma flow decreased from 242 ± 122 to 222 ± 110 ml/min/1.73 m^2 ($p < 0.05$). There was no correlation between changes in glomerular filtration rate and renal plasma flow after indomethacin administration. It is concluded that 1 dose of a nonsteroidal anti-inflammatory drug may cause marked and clinically important alterations in renal function in patients with heart failure. However, the decrease in glomerular filtration rate is not caused by the decrease in renal plasma flow.

894

Clinical Characteristics of Patients in Studies of Left Ventricular Dysfunction (SOLVD)

David Johnstone, Marian Limacher, Michel Rousseau, Chang-Seng Liang, Lars Ekelund, Michael Herman, Douglas Stewart, Maureen Guillotte, Gina Bjerken, William Gaasch, Peter Held, Joel Verter, Dawn Stewart, and Salim Yusuf for the SOLVD Investigators

The Studies of Left Ventricular (LV) Dysfunction (SOLVD) trial consists of 2 large, separate trials, the treatment trial and the prevention trial. Patients with LV ejection fractions ≤ 0.35 and symptoms of congestive heart failure (CHF) were enrolled in the treatment trial, whereas those with no history of overt CHF were enrolled in the prevention trial. The clinical characteristics of patients at baseline in these 2 separate but

Continued on page A30

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concurrent trials are described. Overall, ischemic heart disease was the primary cause of LV dysfunction in both the prevention (83%) and treatment (71%) trial patients. Treatment trial patients had proportionately more women and non-Caucasians than prevention trial patients. Treatment trial patients were more likely to have clinical signs associated with CHF, and had a lower LV ejection fraction (0.25 ± 0.07 vs 0.28 ± 0.06; $p < 0.001$) than prevention trial patients. Clinical characteristics of patients in both trials were further influenced by gender and race. The SOLVD baseline database demonstrates the varied clinical features of severe LV dysfunction and highlights the impact of symptomatic status, gender and race on clinical presentation.

VALVULAR HEART DISEASE

901

Prevalence of Anticardiolipin Antibody in Isolated Mitral or Aortic Regurgitation, or Both, and Possible Relation to Cerebral Ischemic Events

Denise Barbut, Jeffrey S. Borer, Azuddin Gharavi, Donald Wallerson, Richard B. Devereux, Phyllis Supino, and Nicholas D. A. Suite

Anticardiolipin antibodies (acLa) have been associated with cardiac valve abnormalities among patients with and without systemic lupus erythematosus. A relation between acLa, cerebral ischemic events and valve abnormalities has been suggested. To establish the prevalence of acLa in patients with valve disease without lupus and to assess the influence of acLa on the risk of cerebral events in valve disease, 87 consecutive patients with mitral or aortic regurgitation, or both, and 24 normal subjects underwent enzyme-linked immunosorbent assay testing for immunoglobulin G (IgG) and M acLa. AcLa values ≥3 SD above the normal mean were considered "positive." Of 87 patients, 26 had positive IgG acLa compared with 0 of 24 normal subjects ($p < 0.01$); 13 patients had positive immunoglobulin M acLa compared with 2 normal subjects ($p =$ not significant). Focal cerebral events previously occurred in 8 patients (embolic or probably embolic in 7) including 7 of 26 IgG acLa-positive and 1 of 60 IgG acLa-negative patients ($p < 0.001$). Thus, in the absence of lupus, IgG acLa is highly prevalent among patients with aortic or mitral regurgitation, or both; this association may indicate a relatively high risk for cerebral embolic events.

CARDIOMYOPATHY

906

Effects of Calcitonin Gene-Related Peptide on Cardiac Contractility, Coronary Hemodynamics and Myocardial Energetics in Idiopathic Dilated Cardiomyopathy

Jean Luc Dubois-Randé, Pascal Merlet, Christophe Benvenuti, Said Sediame, Isabelle Macquin-Mavier, Etienne Chabrier, Pierre Braquet, Alain Castaigne, and Serge Adnot

Cardiac effects of calcitonin gene-related peptide were assessed in 9 patients with idiopathic dilated cardiomyopathy. Calcitonin gene-related

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peptide was administered consecutively in the left main coronary artery at incremental infusion rates of 15, 50, 150 and 600 pmol · min^{-1}. Hemodynamics improved only in response to the 2 highest infusion rates, which were associated with an increase in cardiac index and a decrease in both systemic arterial and filling pressures. These changes were associated with a significant increase in plasma norepinephrine and epinephrine concentrations and with a decrease in plasma atrial natriuretic factor concentration. Peak positive first derivative of left ventricular pressure remained unchanged at any infusion rate. Coronary blood flow increased only at the 2 highest infusion rates, whereas coronary resistance decreased. Thus, calcitonin gene-related peptide has no direct effect on cardiac contractility. No coronary vasodilating effect was observed at low doses which were not associated with systemic effect of the peptide.

913

Influence of Left Ventricular Hypertrophy and Function on the Occurrence of Ventricular Tachycardia in Hypertrophic Cardiomyopathy

Athanase Dritsas, David Gilligan, Eftichia Sbarouni, Celia M. Oakley, and Petros Nihoyannopoulos

Sixty-nine patients with hypertrophic cardiomyopathy were studied by 2-dimensional and Doppler echocardiography and 72-hour ambulatory monitoring to examine the relation between the degree of left ventricular (LV) hypertrophy and dysfunction and the occurrence of ventricular tachycardia (VT). Episodes of nonsustained VT were detected in 29% of patients. The magnitude of LV hypertrophy and the degree of LV systolic or diastolic dysfunction were similar in patients with and without VT. These findings suggest a dissociation between the arrhythmogenic substrate in hypertrophic cardiomyopathy and its echocardiographic features.

CONGENITAL HEART DISEASE

917

Front-Loading of Double-Umbrella Devices, a New Technique for Umbrella Delivery for Closing Cardiovascular Defects

Stanton B. Perry and James E. Lock

In all, 22 defects (6 atrial septal, 13 ventricular septal, 2 patent ductus arteriosus and 1 coronary artery fistula) in 17 patients were closed with double umbrellas using a new delivery technique, front-loading. The defect was successfully closed in all patients, including 5 in whom standard delivery techniques were unsuccessful. Front-loading of double umbrellas will enable further miniaturization of umbrella delivery systems and expand the range of available delivery sheaths, and may improve delivery of double-umbrella devices to inaccessible parts of the circulation.

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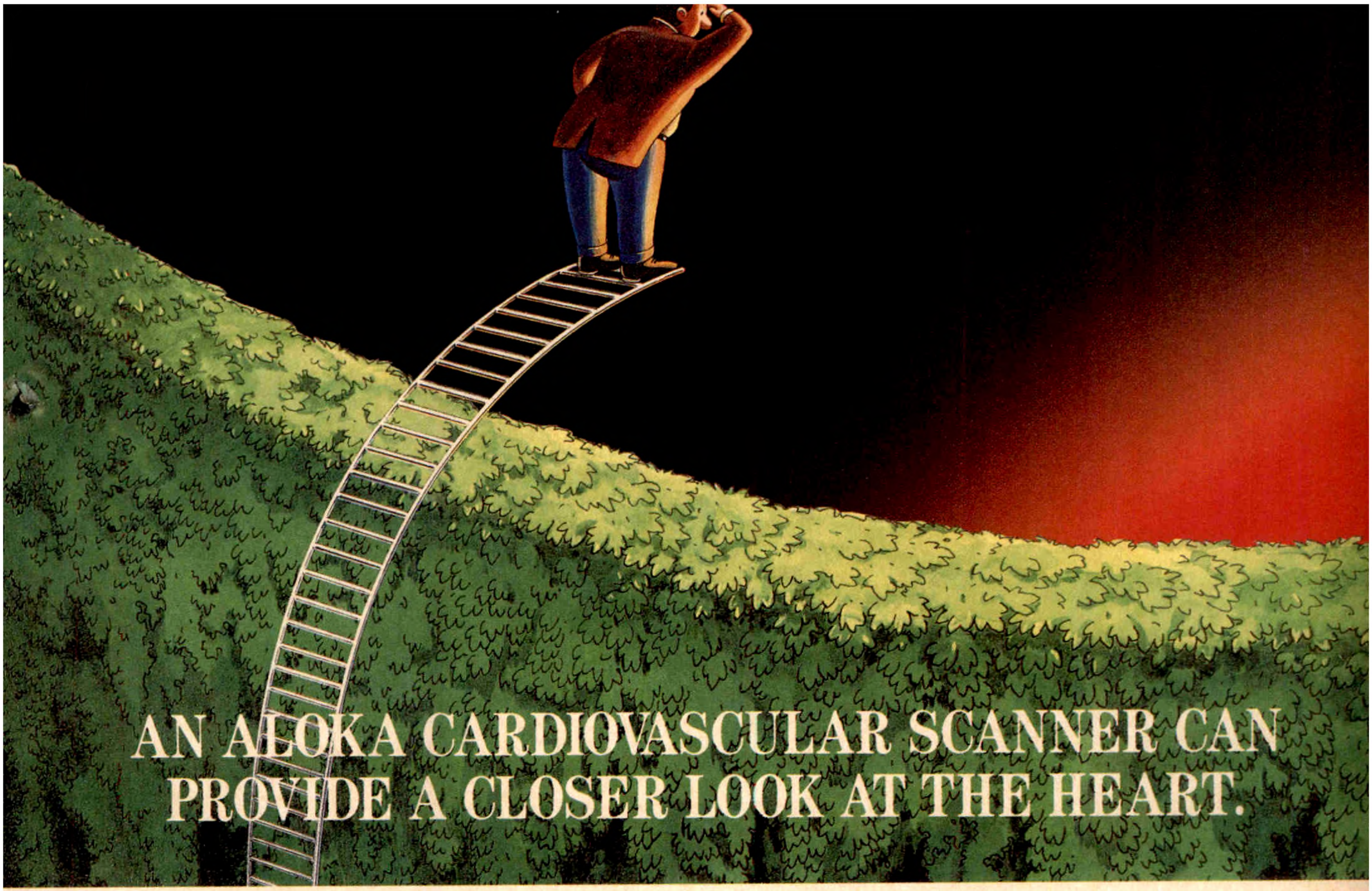

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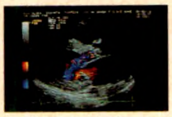

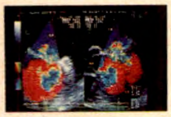

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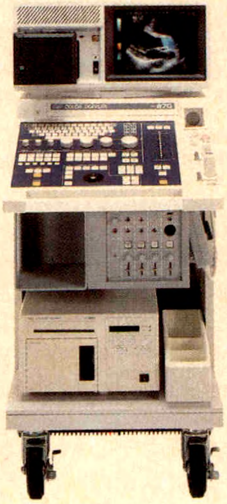

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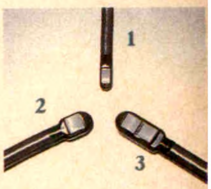

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MISCELLANEOUS

921

Cardiomyopathy of Obesity: A Clinicopathologic Evaluation of 43 Obese Patients with Heart Failure

Edward K. Kasper, Ralph H. Hruban, and Kenneth L. Baughman

Right heart hemodynamic and endomyocardial biopsy abnormalities associated with marked obesity were characterized in 43 patients with dilated cardiomyopathy and compared with 409 lean patients with similar symptoms at presentation. Marked obesity was defined as a body mass index ≥ 35 kg/m^2. Marked obesity was not uncommon in a group of patients with dilated cardiomyopathy and was associated with higher filling pressures, pulmonary vascular resistance and cardiac output than in lean patients with similar degrees of left ventricular dysfunction. No etiology was found to account for the cardiomyopathy in 76.7% of the obese group compared with the lean group where a cause for the cardiomyopathy was found in 64.5% of the patients. These data suggest that the cardiomyopathy of obesity may play an important role in a population referred for the evaluation of cardiomyopathy.

925

Transesophageal Echocardiographic Diagnosis of Right-Sided Cardiac Masses in Patients with Central Lines

Gerald I. Cohen, Allan L. Klein, Kwan-Leung Chan, William J. Stewart, and Ernesto E. Salcedo

Transesophageal echocardiographic diagnosis of right heart masses was examined in 19 adult patients with central venous catheters and permanent pacemakers. Frequent clinical features of the group included sepsis (especially with staphylococcus), recent surgery, bowel disease and myocardial infarction. Transthoracic echocardiography was unreliable and occasionally misleading, usually because of poor image quality and inadequate visualization of the superior vena cava; these limitations were overcome by transesophageal echocardiography. Transesophageal echocardiographic findings were useful in directing the management of patients, especially by guiding surgery, anticoagulation, antibiotic administration and line removal. Transesophageal echocardiography should be considered in patients with central lines, a negative transthoracic study, and sepsis or thromboembolism of unknown origin.

930

Left Ventricular Response to Submaximal Exercise in Endurance-Trained Athletes and Sedentary Adults

John R. Schairer, Paul D. Stein, Steven Keteyian, Frank Fedel, Jonathan Ehrman, Moshin Alam, Jerald W. Henry, and Tracy Shaw

Upright bicycle exercise was performed by 17 endurance-trained male athletes and 15 sedentary men. M-mode echocardiograms were obtained during submaximal exercise at predetermined heart rates. Athletes increased cardiac output through a more prominent augmentation of stroke volume than sedentary subjects at submaximal exercise. This was accom-

Continued on page A39

plished through an augmentation of left ventricular end-diastolic volume. This may have a conserving effect on myocardial oxygen consumption at these levels of exercise.

934

Prognostic Value of Echocardiography in Hospitalized Patients with Pericardial Effusion

Mark J. Eisenberg, Keith Oken, Salvador Guerrero, Mohammad Ali Saniei, and Nelson B. Schiller

The prognostic value of echocardiography was studied in 187 hospitalized patients with pericardial effusion. While in the hospital, 9 patients (5%) had cardiac tamponade and 16 (9%) had cardiac tamponade, pericardiocentesis and/or surgical drainage (combined end point). By univariate analysis, effusion size, right ventricular collapse, right atrial collapse, and inferior vena cava (IVC) plethora with blunted response to respiration were each associated with both cardiac tamponade and the combined end point ($p \leq 0.01$ for size and right-sided chamber collapse; $p \leq 0.07$ for IVC plethora). With logistic regression modeling, after effusion size was entered, neither right-sided chamber collapse nor IVC plethora retained significant associations. It is concluded that echocardiographically determined effusion size is a powerful predictor of outcome in hospitalized patients with pericardial effusion, and that right-sided chamber collapse and IVC plethora with blunted response to respiration add little if any additional prognostic information.

METHODS

940

A New Method for Evaluating Lung Uptake of Thallium-201 During Stress Myocardial Scintigraphy

Giorgio Baccelli, Sergio Terrani, Paolo Pacenti, Ezio Omboni, Mario Bergonzi, Paolo Reggiani, Michele Catalano, and Roberto Bianchi

A low-cost, reliable device that allows left ventricular dysfunction to be detected very easily and quickly is described. This new, noninvasive device exploits miniature lightweight scintillation probes that can be fixed to the patient's skin and held comfortably in place by simple adhesive tape. These probes allow changes in thallium lung uptake to be continuously and simultaneously recorded as time-activity curves over sustained periods of time irrespective of the posture and the physical activity performed by the patient. These time-activity curves display a clear-cut peak and plateau; the peak/plateau ratio is proposed as an easy-to-obtain index for identifying patients with normal and impaired left ventricular performance.

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CORONARY ARTERY DISEASE

The American Journal of Cardiology

OCTOBER 1, 1992, VOL. 70, NO. 9

Clinical, Hemodynamic, Electrocardiographic and Mechanical Events During Nonocclusive, Coronary Atherectomy and Comparison with Balloon Angioplasty

Gregory S. Pavlides, MD, Andrew M. Hauser, MD, Cindy L. Grines, MD,
Patricia I. Dudlets, RDMS, and William W. O'Neill, MD

The periprocedural events and myocardial function during nonocclusive coronary atherectomy by Rotablator or transluminal extraction catheter (TEC) may differ from events during balloon angioplasty. This may have important clinical consequences and needs to be defined further. Therefore, 17 patients undergoing Rotablator and 18 undergoing TEC atherectomy were assessed by clinical, hemodynamic and electrocardiographic monitoring and simultaneous transesophageal echocardiography. The findings were compared with similar parameters during subsequent balloon angioplasty performed in 16 of 17 patients undergoing Rotablator and 14 of 18 undergoing TEC atherectomy. Chest pain occurred more frequently during balloon inflation than during either atherectomy ($p < 0.02$), whereas ST-segment and T-wave electrocardiographic changes were equally frequent. Transient second- or third-degree atrioventricular block occurred in 6 patients during Rotablator but in none during TEC atherectomy or balloon inflation ($p < 0.01$ for each). Hemodynamic parameters and global left ventricular function remained unchanged during atherectomy. Regional myocardial function in the distribution of the target coronary artery, assessed by a wall motion score, was not affected during Rotablator, but deteriorated slightly during TEC atherectomy and more significantly during balloon inflation (score from 0.3 ± 0.5 to 1.0 ± 0.7 during TEC and 2.0 ± 0.6 during balloon inflation, $p < 0.005$ for both). Thus, chest pain is infrequent, whereas hemodynamics and global left ventricular function are preserved during Rotablator and TEC atherectomy. Transient atrioventricular block during Rotablator and regional myocardial dysfunction during TEC atherectomy may occur without significant consequences. These data suggest that these techniques may be preferable to balloon angioplasty for preserving intraprocedural left ventricular function.

(Am J Cardiol 1992;70:841-845)

In an effort to overcome the limitations of balloon coronary angioplasty, new transcatheter therapeutic techniques have been developed. In the mid-1980s removal of atheromatous material from the peripheral and subsequently coronary arteries by a directional atherectomy catheter first became possible.[1,2] Since then, 2 other atherectomy catheters have been introduced; the transluminal extraction catheter (TEC)[3] and the Auth Rotablator.[4,5] Although fundamentally different, the last 2 catheters are nonocclusive, working by rotational cutting without balloon inflation. As such, these devices do not interrupt coronary blood flow and might preserve myocardial function during atherectomy. This may have important clinical consequences. Since the periprocedural events during rotational atherectomy have not been described, we studied 17 patients undergoing Rotablator atherectomy and 18 patients undergoing TEC atherectomy from our early atherectomy experience using hemodynamic, electrocardiographic and transesophageal echocardiographic monitoring. Most of these patients (16 of 17 undergoing Rotablator and 14 of 18 undergoing TEC atherectomy) received adjunctive balloon angioplasty, so the findings for each device during atherectomy were compared with findings during balloon inflation.

METHODS

Atherectomy devices: The Rotablator and TEC devices have been described in detail elsewhere.[6,7] In brief, The TEC (Interventional Technologies, Inc., San Diego, California) is a percutaneously introduced flexible-torque tube that tracts over a steerable 0.014-inch guidewire and through a 10.5Fr guiding catheter to the target lesion in the coronary artery or graft. A conical

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cutter is present at the distal tip of the catheter. When the radiopaque tip is properly positioned near the origin of the lesion, a trigger is activated on a hand-held control piece. This trigger causes the conical cutter to rotate at 750 rpm while, simultaneously, suction is applied through the opening of the cutting windows to extract the fragments of the plaque through the catheter. At the top of the control piece, a sliding thumb lever is used for controlling the anterograde excursion of the cutter over the guidewire. Immediately before atherectomy, a warmed lactated Ringer's solution is flushed through the guiding catheter under 180 mm Hg pressure. Plaque material extracted from the artery is collected in a glass vacuum reservoir. A remote battery pack provides power to the device.

The Rotablator atherectomy device consists of a rotational abrasive burr attached to a long flexible drive shaft tracking over a central flexible 0.009-inch stainless steel guidewire. The burr has an elliptical shape with fine diamond abrasive particles embedded into the distal half; various burr sizes are available for coronary use. Compressed air or nitrogen powers a turbine motor that delivers rotational energy to the burr through the drive shaft. The speed of burr rotation is high (190,000 rpm) and is controlled by the air pressure that is activated by a foot pedal. During rotation, a small volume of sterile saline solution irrigates the catheter sheath to lubricate and cool the rotating system. After the guidewire crosses the lesion, the burr is advanced to the origin of the lesion and then the rotating burr is advanced through the lesion. Because most particles are smaller than 5 to 10 μ, they travel downstream through the capillary system and eventually are trapped in the reticuloendothelial system.

Procedures: All procedures were performed in the cardiac catheterization laboratory. Both atherectomy procedures were approved by the Institutional Review Board and informed consent was obtained for both atherectomy and transesophageal echocardiography. Central aortic and femoral arterial pressures were continuously monitored during the procedures. Six-lead electrocardiograms were recorded in each procedural stage. In all but 3 patients transesophageal echocardiography was performed during the procedure. A commercially available transesophageal echo-probe incorporating a 5 MHz imaging transducer was used with a Sonos 500 imaging system (Hewlett-Packard Corporation). A 2.5 MHz transthoracic transducer was used for the remaining 3 cases. All echocardiographic studies were recorded on ½ inch videotape. The system's soundtrack was used for precise timing of the events.

All patients were awake during their procedure and were premedicated with diazepam (3 mg) and hydromorphone (1 mg) administered intravenously. All were pretreated with aspirin, 325 mg/day orally, and received 10,000 U of heparin intravenously after the arterial and venous sheaths were in place. The guiding catheters (10.5Fr for the TEC and 9Fr for the Rotablator) were advanced to the target coronary artery and baseline coronary angiography was performed. Before the lesion was crossed with the guidewire, additional diazepam (5 mg) was given intravenously, oropharyngeal anesthesia with benzocaine 20% spray (Hurricane, Beutlich Inc., Niles, Illinois) was applied and the transesophageal echo-probe was introduced. The optimal left ventricular short-axis view at the papillary muscle level was obtained and maintained throughout the procedure. A similar view was obtained in the 3 patients in whom transthoracic echocardiography was performed. After baseline measurements were recorded, the lesion was crossed with the guidewire and TEC or Rotablator atherectomy was performed. After completion of the atherectomy, if angiographically indicated, balloon angioplasty was performed. Clinical, hemodynamic, electrocardiographic and echocardiographic data were recorded during atherectomy, during balloon inflation and after procedural completion.

Data analysis: Each atherectomy group (TEC or Rotablator) was analyzed separately. Chest pain was recorded as present or not without severity grading. All changes in standard 6-lead electrocardiograms during each procedural stage were compared with baseline. Global left ventricular function was assessed by the echocardiographically obtained fractional area change (%FAC). This was derived by the equation:

$$\mathrm{FAC} = \frac{\mathrm{LVAd} - \mathrm{LVAs}}{\mathrm{LVAd}} \times 100$$

where left ventricular area in diastole (LVAd) and systole (LVAs) were measured by endocardial tracing. The wall motion of myocardial regions perfused by the target vessels was assigned a wall motion score[8] by 2 echocardiographers (consensus agreement) with 0 = normal, 1 = hypokinesia, 2 = akinesia and 3 = dyskinesia. Three regions were identified in the short-axis view, each perfused by a major epicardial vessel.

Statistical analysis: A commercially available statistical package (Wallonick Associates, Minneapolis, Minnesota) was used for analysis. Analysis of variance was used to measure differences in quantitative parameters between 3 points (baseline, atherectomy, balloon inflation). The Fisher exact test was used for changes in categorical variables during atherectomy or balloon angioplasty from baseline. The Student *t* test was used for comparisons between the 2 atherectomy groups.

RESULTS

Baseline characteristics and procedural outcome: Seventeen patients undergoing Rotablator and 18 undergoing TEC atherectomy were studied. Baseline, clinical and angiographic characteristics were similar between the 2 groups (Table I). Procedural characteristics are listed in Table II. One patient underwent a 2-vessel Rotablator atherectomy (left anterior descending and left circumflex), whereas all remaining patients underwent 1-vessel atherectomy. The Rotablator burr size ranged from 1.25 to 2.25 mm. When multiple burrs were used, the size was sequentially increased. The smallest TEC cutter used was 5.5Fr (1.8 mm) and the largest was 7Fr (2.3 mm). In 9 patients, 1 cutter was used and in 9 patients ≥2 cutter sizes were used. After lesion debulking was achieved, in the majority of cases in both groups balloon angioplasty followed atherec-

TABLE I Rotablator and TEC Coronary Atherectomy: Baseline Patient Characteristics

	Rotablator	TEC
No. of patients	17	18
Age (mean ± SD, years)	60 ± 11	59 ± 12
Men/women	12/5	16/2
Angina class (NYHA)	3 ± 1	3 ± 1
Previous myocardial infarction	8	10
Previous balloon angioplasty	6	5
Previous coronary bypass	4	6
Abnormal electrocardiogram	16	16
No. of coronary arteries narrowed > 50% in diameter	2 ± 1	2 ± 2
Ejection fraction (%)	53 ± 7	49 ± 14

NYHA = New York Heart Association; TEC = transluminal extraction catheter.

TABLE II Rotablator and TEC Atherectomy: Procedural Characteristics

	Rotablator (n = 17)	TEC (n = 18)
Target vessel		
Left main	6	2
Left anterior descending	5	4
Left circumflex	1	3
Right	6	5
Saphenous vein graft*	0	4
Cardiopulmonary or coronary sinus retroperfusion support	3	2
No. of atherectomy catheters per lesion	1.2 ± 0.5	1.6 ± 0.7
No. of passes per catheter used	5 ± 3	6 ± 4
Adjunctive balloon angioplasty	16	14
Successful outcome	17	16
Initial stenosis (mean ± SD)	84 ± 9%	86 ± 10%
Final stenosis (mean ± SD)	13 ± 5%	17 ± 9%

*p = 0.05
TEC = transluminal extraction catheter.

tomy in order to achieve an optimal angiographic result. There was 1 death and one case in which emergency coronary artery bypass graft surgery was required in the TEC group. One patient in the Rotablator group had a slight increase in cardiac enzymes. (CK 135 U with 6.8% MB fraction).

Clinical, hemodynamic, electrocardiographic events and global left ventricular function: Among patients undergoing Rotablator atherectomy, more patients experienced chest pain during balloon inflation than during atherectomy (7 of 16 vs 1 of 17 respectively, $p < 0.02$), whereas ST-segment and T-wave electrocardiographic changes were similar (4 of 16 vs 3 of 17). Transient second- or third-degree atrioventricular block was observed during Rotablator atherectomy in 6 patients. It occurred during atherectomy of either right coronary arteries or dominant circumflex. It did not cause hemodynamic compromise and converted quickly to sinus rhythm without need for temporary pacing. Because the atrioventricular block was transient, it was not calculated into the heart rate reported during Rotablator atherectomy. Among patients undergoing TEC atherectomy, chest pain was also experienced more frequently during balloon inflation than during atherectomy (10 of 14 vs 3 of 18, $p < 0.005$), whereas ST-segment and T-wave electrocardiographic changes were similar (6 of 14 vs 2 of 18, $p = 0.1$). The hemodynamic data during atherectomy and balloon angioplasty are listed in Table III.

TABLE III Hemodynamic Events During Atherectomy and Balloon Angioplasty

	Baseline	Atherectomy	Balloon Angioplasty
Rotablator group			
No. of patients	17	17	16
Heart rate (beats/min)	80 ± 17	78 ± 27	75 ± 17
Systolic blood pressure (mm Hg)	133 ± 24	119 ± 24	115 ± 30
Diastolic blood pressure (mm Hg)	71 ± 12	69 ± 16	71 ± 13
Mean blood pressure (mm Hg)	89 ± 18	87 ± 16	85 ± 17
Fractional area change (%)	45 ± 12	44 ± 16	51 ± 16
TEC atherectomy group			
No. of patients	18	18	14
Heart rate (beats/min)	81 ± 16	80 ± 15	80 ± 19
Systolic blood pressure (mm Hg)	129 ± 15	128 ± 20	126 ± 31
Diastolic blood pressure (mm Hg)	74 ± 14	78 ± 13	81 ± 15
Mean blood pressure (mm Hg)	93 ± 12	95 ± 13	96 ± 17
Fractional area change (%)	52 ± 12	47 ± 18	40 ± 12

TEC = transluminal extraction catheter.

Regional myocardial function: Among patients undergoing Rotablator atherectomy, regional myocardial function of areas perfused by the target coronary arteries did not change significantly during atherectomy, but worsened during subsequent balloon inflation (regions became akinetic [mean score 2 ± 0.7, $p < 0.0001$]) (Figure 1). In patients undergoing TEC atherectomy, regional myocardial function worsened slightly during atherectomy (regions became hypokinetic [mean score 1 ± 0.7, $p < 0.005$]) and more significantly during subsequent balloon inflation (regions became akinetic [mean score 2 ± 0.7, $p < 0.0001$]) (Figure 2).

Differences between Rotablator and transluminal extraction catheter atherectomy: Two important differences between Rotablator and TEC atherectomy were observed. First, transient second- or third-degree atrioventricular block was observed only during Rotablator atherectomy (6 of 17 vs 0 of 18, $p < 0.01$). Second, regional myocardial function decreased more during TEC atherectomy than during Rotablator atherectomy (score 1 ± 0.7 vs 0.5 ± 0.7, $p < 0.05$). Regional myocardial dysfunction during TEC atherectomy was transient, however, with myocardial function returning to baseline after atherectomy.

DISCUSSION

Clinical and hemodynamic events: The periprocedural events during balloon coronary angioplasty have been described.[9] Despite the small number of patients studied in this series, it appears that nonocclusive rotational atherectomy is associated with less periprocedural myocardial ischemia than to balloon coronary angioplasty. However, nonocclusive atherectomy does not appear to eliminate completely periprocedural ischemia since electrocardiographic ST-segment and T-wave changes were observed with equal frequency during atherectomy and balloon inflation. However, the decreased symptom level and better preserved myocardial function during atherectomy may be clinically important because severe chest pain and worsened myocardial function during balloon inflation frequently preclude prolonged inflations which may be required for an optimal angiographic result.

Transient atrioventricular block (second- and third-degree) was relatively frequent during Rotablator atherectomy. Segmental ischemia alone does not explain the underlying mechanism, because regional myocardial function was preserved during atherectomy and none of these patients developed atrioventricular block during balloon inflation. Several other mechanisms have been suggested. Focal embolization of minute particles generated by the Rotablator could be responsible. Friedman et al[10] had previously shown in an animal model that such microembolization of Rotablator microparticles at distal vascular beds can occur without significant alteration of contractile function. It has also been suggested that microcavitation created by the rotating burr is responsible.[11] The mechanical or "vibratory" effect of the rotating burr provides another potential mechanism.

Hemodynamic response to occlusive balloon inflations in patients undergoing angioplasty depends on baseline left ventricular function.[12] Preservation of hemodynamics during balloon inflations and atherectomy in our patients most likely reflects near-normal baseline left ventricular function.

Myocardial contractile function: Myocardial contractile function of regions perfused by the target coronary arteries remain the most sensitive indicator of ischemia during atherectomy or balloon inflation.[8] Several studies have demonstrated that regional akinesia or dyskinesia invariably follows balloon occlusion. A similar response during balloon inflation was observed in our patients in both groups, although balloon angioplasty after atherectomy may not be similar to balloon angioplasty alone. Among patients undergoing Rotablator atherectomy, preservation of regional myocardial function during atherectomy suggests relative preservation of myocardial perfusion. Our data also suggest that regional ischemia occurs during TEC atherectomy, but to a lesser degree than during occlusive balloon inflation. The mechanism for ischemia during TEC atherectomy may be in part related to the lactated Ringer's

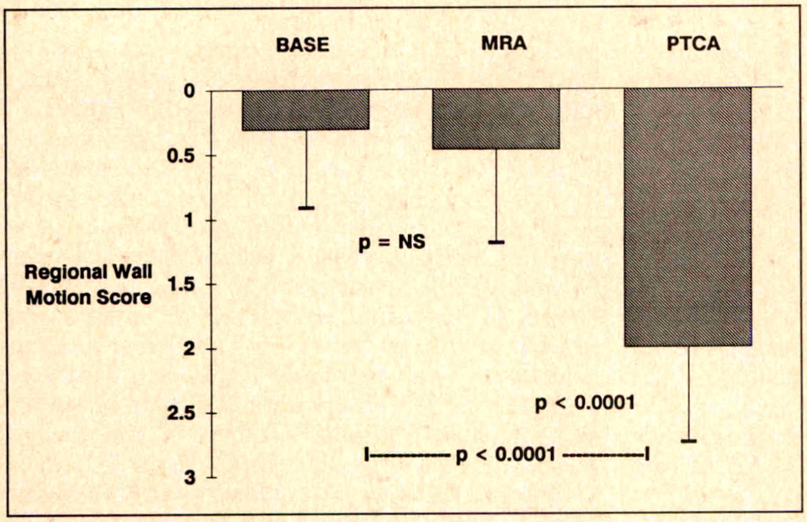

FIGURE 1. Wall motion score of regions perfused by the target vessels during mechanical Rotablator atherectomy (MRA) and during subsequent adjunctive percutaneous transluminal coronary angioplasty (PTCA) in patients undergoing Rotablator atherectomy. 0 = normal; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia; NS = not significant.

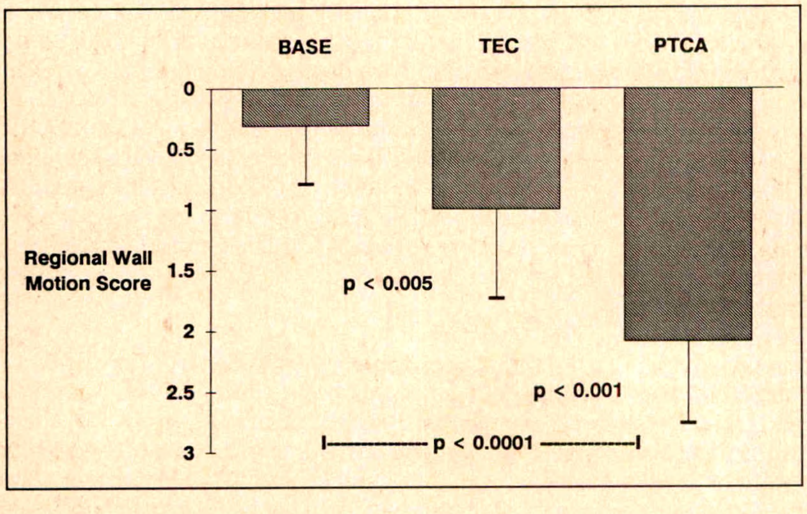

FIGURE 2. Wall motion score of regions perfused by the target vessels, during transluminal extraction catheter (TEC) atherectomy and during subsequent adjunctive percutaneous transluminal coronary angioplasty (PTCA) in patients undergoing TEC atherectomy. 0 = normal; 1 = hypokinesia; 2 = akinesia; 3 = dyskinesia.

fluid solution used during atherectomy. Reduction in coronary blood flow may also occur because of partial occlusion by the catheter and continuous suction of the atheromatous pieces along with blood through the device. Catheter sizes during TEC atherectomy appear to be an important factor since in 2 patients regional myocardial dysfunction was observed with larger catheters (7Fr) but not smaller ones.

Clinical implications: The data may aid in the selection of the appropriate atherectomy catheter for clinical use. The occurrence of transient atrioventricular block associated with the Rotablator may dictate prophylactic placement of a temporary pacemaker in patients with known atrioventricular node disease or in those with the right or dominant circumflex as the target coronary artery. The absence of significant suppression of myocardial function during Rotablator atherectomy, and only mild suppression during TEC atherectomy, make these devices attractive for treating patients with large area of myocardium supplied by the target coronary artery as in the case of patients with left main disease. Although this benefit appears theoretical because the majority of patients underwent adjunctive balloon angioplasty, in many cases the result achieved by the atherectomy alone is adequate (diameter stenosis <50%), and rotational atherectomy can be used as a stand-alone technique.

Study limitations: This study was undertaken to assess the periprocedural events during Rotablator and TEC atherectomy compared with balloon coronary angioplasty. It was not intended to be an assessment of the clinical value of each technique involved, since the numbers are small and the patients studied represent our early experience and only a small sample of a larger cohort of patients treated by Rotablator or TEC atherectomy.

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Effects of Exercise Test Results on Physician Perceptions of Coronary Artery Disease Probability Using a Threshold Analysis

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The incremental diagnostic value of exercise electrocardiographic testing compared with clinical data alone in the diagnosis of coronary artery disease (CAD) was found to be of limited value in a previous study. That study used a computer algorithm for diagnosing disease. Thus, the strict use of the results apply only to computerized disease diagnosis rather than physicians' diagnoses. The aim of the present study was to determine whether exercise test data improve a physician's ability to detect the presence or absence of CAD and 3-vessel or left main CAD, and whether the data effect the decision to perform angiography. The study sample comprised a data base of 312 patients whose clinical data, exercise test results and coronary anatomy were known. Individual cases were presented to 8 cardiologists with and without exercise data. The cardiologists provided estimates of disease probability and were asked whether they would request coronary angiography. Receiver-operating characteristic curves and goodness-of-fit analysis showed better discrimination and calibration of the estimates for the presence of CAD and 3-vessel/left main CAD after exercise test results were known. Individualized probability thresholds for deciding whether to request angiography were determined for each physician. Forty-three percent of patients crossed ≥1 threshold, with 64% of the crossings in the correct direction. For estimating the presence of any CAD, 84% of crossings from below to above a threshold were correct, whereas only 36% from above to below were correct. For 3-vessel/left main CAD, 36% of crossings from below to above a threshold were correct, whereas 88% from above to below were correct. Fifty-two percent of patients with 3-vessel/left main CAD were above a threshold for angiography before stress testing compared with 68% post-test, with 15 additional patients with 3-vessel or left main CAD above thresholds post-test. Thus, exercise testing is useful in the diagnosis of CAD and particularly in the selection of patients with 3-vessel or left main CAD for angiography.

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The incremental diagnostic value of exercise testing compared with clinical data alone for the diagnosis of coronary artery disease (CAD) has been studied by Goldman.[1] Assessments of disease probability were generated from clinical data before and after the addition of exercise test information, using a computer-derived logistic regression model applied to information from 324 consecutive angiographic referrals at Brigham and Women's Hospital. Changes in computer-derived probability estimates resulting from the addition of exercise test data were assessed using a threshold approach. The number of subjects whose probability assessments correctly and incorrectly crossed decision-making thresholds were tabulated. It was concluded that few of the exercise tests actually resulted in the crossing of a probability threshold and that the direction of threshold crossing was incorrect in one third of cases. Thus, exercise testing in that investigation was of limited value in the diagnosis of CAD. In this study, we evaluated the effect of exercise test results on physician's assessments of CAD probability. We also dichotomously stratified CAD into: (1) any angiographic CAD (≥1 luminal narrowing of >50%) versus no CAD, and (2) left main or 3-vessel CAD versus less severe or no CAD. Finally, we determined the probability thresholds above which a physician would most likely request angiography and used these in a threshold analysis.

METHODS

Study sample: A data base was compiled from consecutive referrals for the evaluation of known or suspected CAD at 2 hospitals (Long Beach Memorial Hospital and Long Beach Veterans Administration Hospital). Data were collected between 1989 and 1990. Of these patients, 312 had exercise tests without cardiac imaging and constitute the study sample. The data evaluated included 14 clinical and 7 exercise test variables (Table I). Each patient also underwent coronary angiography.

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Physician questionnaires: Two series of questionnaires were devised for each patient in the study sample. Each questionnaire included a narrative description of the patient data followed by a series of statements for the physician to complete. One series of questionnaires included clinical and exercise data (parts A and B of Table I); the other included only clinical data (part A of Table I). The following statements were to be completed by the physician reviewing the information: "____% probability of >50% narrowing in at least 1 vessel" and "____% probability of 3-vessel or left main disease." Furthermore, the physician was asked whether he or she would request angiography based on the information presented. The questionnaires were randomly distributed to the participating physicians with the condition that the 2 questionnaires for a given patient were never distributed to the same physician. No 2 physicians received the same data, and each received the same proportion of pre- and post-test cases.

Physicians: Eight physicians agreed to complete the physician questionnaires; all are board-certified cardiologists from our division, with an average of 10 years of clinical experience.

Data analysis: The physicians' probability assessments were evaluated for discriminatory ability with receiver-operating characteristic curve analysis. Concordance of the physicians' estimates of disease prevalence with actual prevalence ("calibration") was assessed with a goodness-of-fit analysis. Finally, a threshold analysis was performed.

Receiver-operating characteristic curve analysis: Receiver-operating characteristic curve analysis[2] was used to test the physician's ability to discriminate CAD (>50% stenosis) from no CAD, and 3-vessel/left main CAD from lesser or no CAD. Curves were derived for pre- and post-test probability estimates in each disease subgroup. A larger area under a curve implies improved ability to discriminate patients with disease. The statistical significance of the difference of the areas under the curves was evaluated with the Hanley-McNeil Z test.[3]

Goodness-of-fit analysis: Calibration is another marker of accurate probability estimation. It relates to how well the probability estimates reflect disease prevalence. If a group of subjects has a 40% CAD prevalence, then calibration is good if the mean of the individual probability estimates is 40%. It is possible to have good discrimination with poor calibration, and vice versa. Calibration was evaluated with the "Goodness of Fit" method[4] as follows: First, the estimates were arranged in ascending order of probability. Then, these ordered estimates were divided into quintiles of equal numbers, and the average estimate in each quintile was calculated. The prevalence of CAD or 3-vessel/left main CAD in each quintile was then subtracted from this average. These differences are measures of the overestimation in each quintile and show how accurate the estimates are at low (quintile 1), intermediate (quintiles 2 to 4) and high (quintile 5) probabilities.

TABLE I Clinical and Exercise Test Variables

Part A: Clinical Variables

(1) Age
(2) Sex
(3) Chest pain type
  (a) Typical angina:
    (1) Upper part of body
    (2) Related to exertion and relieved by rest or nitrates
    (3) Duration > 15 s and < 30 min
  (b) Atypical angina: (1) and either (2) or (3) above
  (c) Nonanginal chest pain: (1), but not (2) or (3) above
  (d) No chest pain: neither (1), (2) nor (3) above
(4) History of hypertension
(5) History of diabetes
(6) History of myocardial infarctions (including dates)
(7) Family history of premature coronary disease
(8) History of smoking (cigarettes/day; no. of years)
(9) Medications at time of exercise testing
  (a) β-adrenergic receptor antagonists
  (b) Digitalis derivatives of digoxin
  (c) Nitrates
  (d) Calcium antagonists
  (e) Diuretics
(10) Fasting plasma glucose > 120 mg/dl
(11) Serum cholesterol level (mg/dl)
(12) Resting electrocardiogram (normal, abnormal, nonspecific ST-segment changes, Q waves present or absent with locations)
(13) Ejection fraction by radionuclide ventriculography
(14) Resting systolic blood pressure

Part B: Exercise Test Variables

(1) Protocol (Bruce, Balke, and so forth)
(2) Duration of test in minutes
(3) METs achieved
(4) Resting and exercise blood pressure and heart rate
(5) Amount of upsloping, downsloping or horizontal ST depression at 80 ms in ml
(6) Presence of exercise-induced angina
(7) Presence or absence of exercise-induced reduction in blood pressure

Threshold analysis[5]: Individualized probability thresholds for any CAD and 3-vessel/left main CAD above which a physician would request angiography were determined for each cardiologist. These thresholds were used to study the effect of exercise test results on recommendation for angiography. We determined whether a physician believed angiography was or was not indicated by his or her response to the multiple choice statement on the questionnaires containing the exercise data (see aforementioned description). The individualized threshold for angiography for any CAD or for 3-vessel/left main CAD was defined as the number p, such that the number of cases with a probability estimate higher than p for which angiography was indicated plus the number of cases with a probability estimate lower than p for which angiography was not indicated was maximized. Thus, individualized probability thresholds for the presence of any significant CAD, as well as 3-vessel/left main CAD, were determined for each physician, above which the physician would recommend angiography, and below which he or she would not.

Threshold analyses were conducted separately for any CAD and for 3-vessel/left main CAD. Subjects were divided into either high or low pretest and high or low post-test probability groups depending on whether the probability assessments were above or below the individualized thresholds before and after the exercise test. Correct threshold crossings are defined as post-test

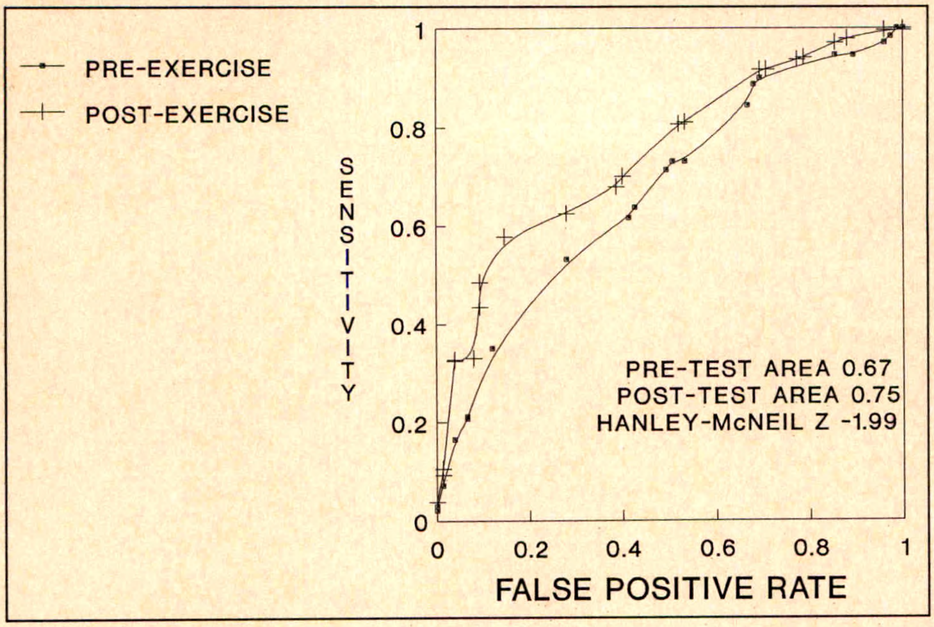


FIGURE 1. Receiver-operating characteristic curves for pre- and post-test estimates of angiographic disease probability. Area under post-test curve is significantly greater than that under pretest curve.

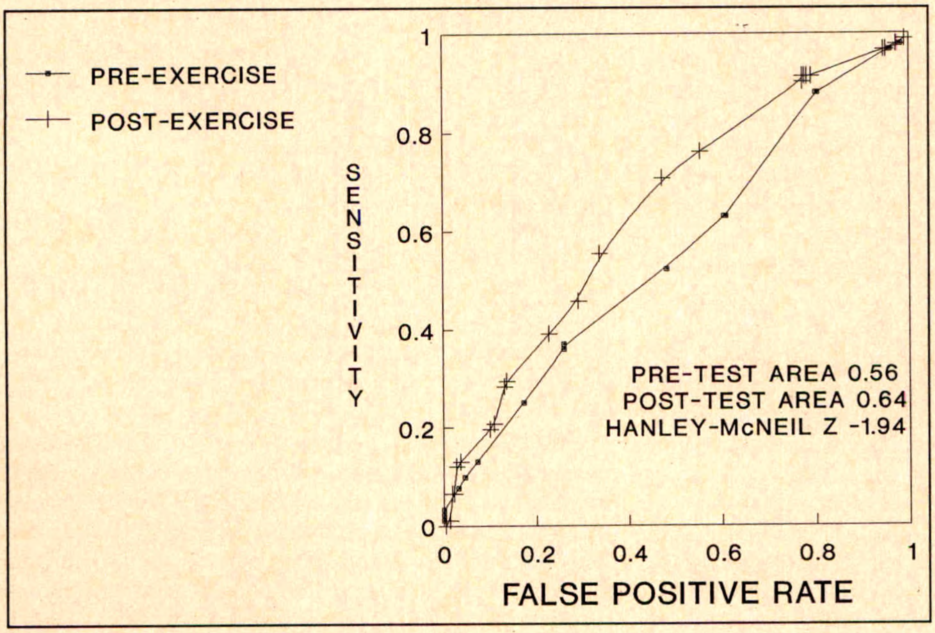


FIGURE 2. Receiver-operating characteristic curves for pre- and post-test estimates of 3-vessel or left main disease probability. Area under post-test curve is significantly greater than that under pretest curve.

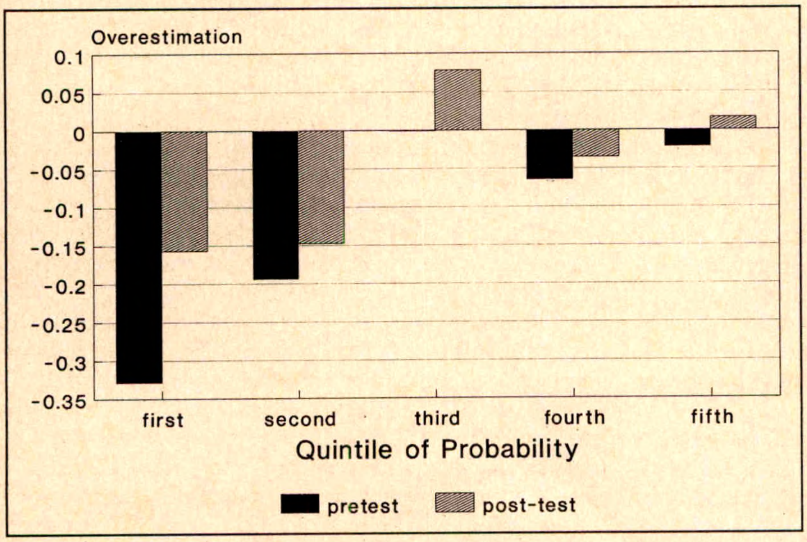


FIGURE 3. Goodness-of-fit analysis for probability estimates for any stenosis >50%.

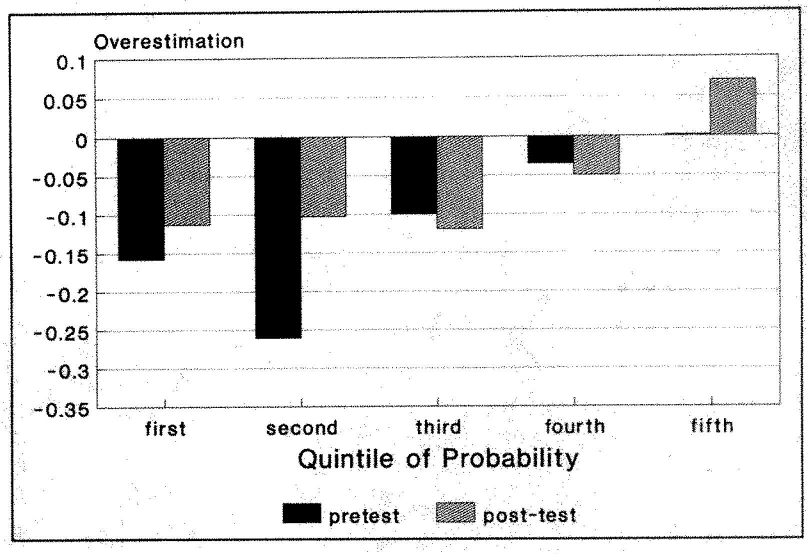


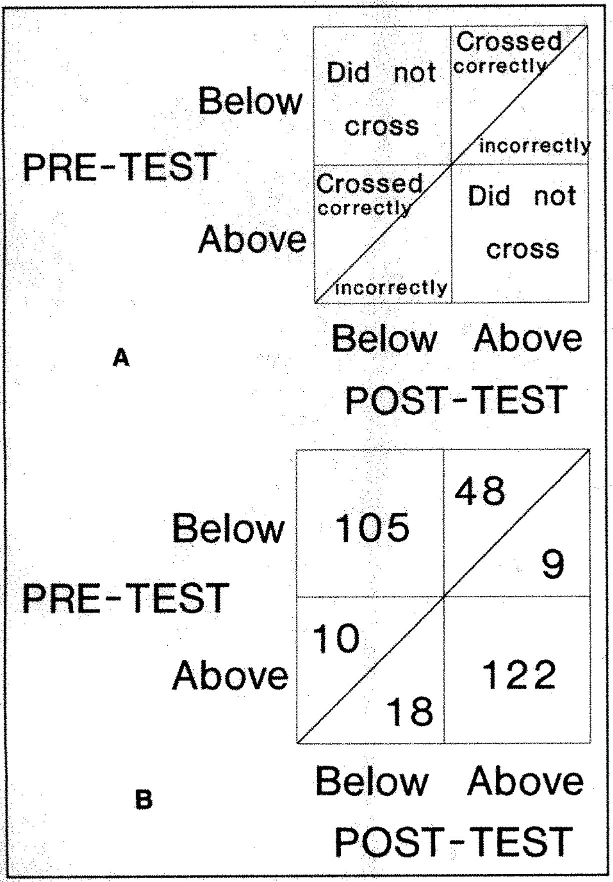
FIGURE 4. Goodness-of-fit analysis for probability estimates for 3-vessel or left main disease.

probabilities, which are more correct (higher in subjects with and lower in those without CAD) than pretest ones. In cases where thresholds were crossed, "correct" and "incorrect" crossings were recorded.

RESULTS

There were 70 subjects (92% men; mean age 61 years) from Long Beach Memorial Hospital and 242 from the Long Beach Veterans Administration Hospital. There was history of myocardial infarction in 18% of patients, and typical angina was described by 58%, atypical angina by 21%, nonanginal pain by 9%, and no chest pain by 12%. On angiography, there was CAD in 76% of patients and 3-vessel or left main CAD in 29%.

Physicians significantly improved their ability to discriminate patients with and without significant CAD when they knew the exercise test results. The difference is shown in Figure 1, where the receiver-operating characteristic curve area increased from 0.67 to 0.75 ($p < 0.05$). Physicians were better at discriminating the presence of any significant angiographic CAD than 3-vessel/left main CAD (Figure 2) (area 0.67 vs 0.56 pretest, and 0.75 vs 0.64 post-test). Figures 3 and 4 show the goodness-of-fit data for the 2 angiographic classifications. Calibration of the estimates improved after exercise testing for both classifications. There was a tendency to underestimate disease probability in the low-probability quintiles. Figure 5 shows the results of the threshold analysis. The average threshold for any angiographic CAD was 69 ± 20%. The average threshold for 3-vessel/left main CAD was 19 ± 9%. Eighty-five of



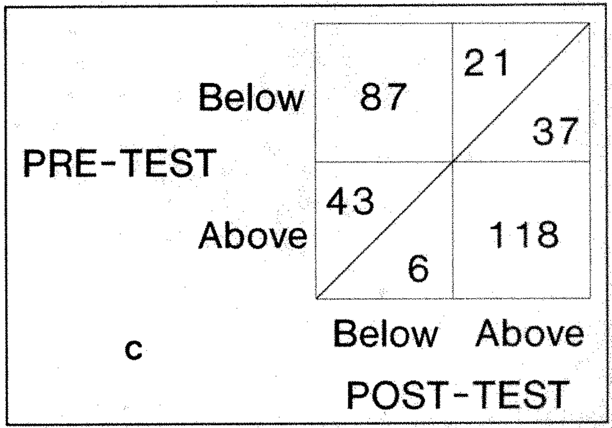


FIGURE 5. Threshold analysis of pre- and post-test probability estimates. Data are displayed separately for any disease *(A)* and 3-vessel or left main disease *(B)*. Numbers of subjects above or below pre- and post-test thresholds are displayed in *1 of 4 quadrants.* In quadrants where thresholds were crossed, numbers of correct and incorrect crossings are displayed separately in *upper left or lower right, or both, portions of quadrant,* respectively *(C)*.

312 subjects (27%) crossed a threshold for any angiographic CAD, and 107 (34%) crossed a 3-vessel/left main CAD threshold. One hundred thirty-five patients crossed ≥ 1 threshold. Overall, 122 of 192 threshold crossings (64%; $p < 0.001$ chi-squared) were in the correct direction. For any CAD, crossings from below to above a threshold were correct in 48 of 57 cases (84%; $p < 0.001$). Crossings from above to below a threshold were correct in only 10 of 28 cases (36%; p = not significant). For 3-vessel/left main CAD, crossings from below to above a threshold were correct in 21 of 58 cases (36%; $p < 0.05$). Crossings from above to below a threshold were correct in 43 of 49 cases (88%; $p < 0.001$). Thus, there were 9 more subjects above thresholds after than before exercise testing (58 crossing from below to above vs 49 from above to below) and 15 more cases of 3-vessel/left main CAD among subjects above a threshold after testing (21 correct vs 6 incorrect crossings). Forty-eight of 92 patients (52%) with 3-vessel or left main CAD were above thresholds pretest, and 63 (68%) were above thresholds post-test ($p < 0.01$).

DISCUSSION

The results of this study confirm that exercise testing improves the statistical discrimination of the presence of CAD. More importantly, the threshold analysis suggests that physicians are able to use exercise test data clinically to more precisely select patients with significant or severe, potentially surgical CAD for angiography. This investigation confirms Goldman's[1] earlier observation that threshold crossings were in the correct direction in approximately two thirds of cases. However, the exercise test was effective in detecting a substantial number of cases of 3-vessel/left main CAD that would have been missed without the procedure. For detecting 3-vessel/left main CAD, exercise testing is useful when the pretest probability is high or low. If the pretest probability is high, the exercise test can provide information that reliably moves a patient into a low-probability group. If the pretest probability is low, exercise testing can predict a substantial number of patients with 3-vessel/left main CAD. Correct estimation of the probability of any angiographic CAD is most useful when angioplasty is being considered. The results show that exercise testing is much more useful when the pretest probability for CAD is below the clinician's threshold for requesting coronary angiography. Therefore, exercise testing results in the detection of many cases of CAD, with few false positives.

It has been demonstrated by numerous other investigators that exercise testing is not helpful in confirming the diagnosis of CAD when the pretest probability is high, because more false than true negatives will be found.[6-11] However, physicians are generally not as interested in the question of diagnosing disease in these subjects as they are in establishing its severity. The results suggest that exercise testing is very useful in this regard.

This investigation differs from the study of Goldman[1] in several ways. First, Goldman used a computer model to generate pre- and post-test probabilities. Because computers are rarely used in practice, the present investigation appears more applicable. Second, in the Goldman study, a series of arbitrary thresholds were used, rather than user-determined thresholds that would more likely be used for decision making. Third, Goldman only addressed the diagnosis of any angiographic CAD. In clinical practice, there is frequently more concern for whether 3-vessel or left main CAD is present. Finally, the threshold crossings in the Goldman study were not analyzed with respect to the direction of crossing. In the present study, crossing of a 3-vessel/left main CAD threshold occurred in the correct direction in only 60% of cases. However, because of the predominance of incorrect crossings from below to above angiography thresholds (rather than from above to below), many cases of severe CAD were detected with few cases missed.

The evaluation of diagnostic tests should mimic their use in everyday clinical practice and assess their incremental value after considering more accessible information.[12] We attempted to fulfill these goals and found that 1 of the most widely used diagnostic tests, though imperfect, is helpful. Our approach is simple and applicable to other cardiac examinations such as Doppler echocardiography for severe aortic stenosis and exercise thallium scintigraphy for evaluating CAD.

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Atherosclerosis of the Aorta and Coronary Arteries and Cardiovascular Risk Factors in Persons Aged 6 to 30 Years and Studied at Necropsy (The Bogalusa Heart Study)

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Race and sex differences in aorta and coronary atherosclerotic lesions were studied in 150 persons aged 6 to 30 years. The intimal surface involvement with aorta fatty streaks was extensive, 0 to 71%, and greater in blacks than in whites (32 vs 20%, p <0.001). Coronary artery fatty streaks were more extensive in male than in female subjects (range 0 to 22%). Fibrous plaque lesions were present but not extensive in either the aorta (0 to 12%) or the coronary artery (0 to 24%) specimens. Lesions were more prevalent in male than in female persons, particularly white male subjects. The relation of fatty streaks to fibrous plaques was greater in the coronary vessels than in the aorta. In male subjects, aorta fatty streaks were strongly related to antemortem levels of total cholesterol, low-density lipoprotein cholesterol and ponderal index in white male subjects. Coronary artery fatty streaks in white male persons were significantly associated with serum triglycerides, very low density lipoprotein cholesterol, systolic and diastolic blood pressure and ponderal index. These results link antemortem risk factors to the development of atherosclerotic lesions and emphasize the need for preventive cardiology in early life.

(Am J Cardiol 1992;70:851–858)

Atherosclerotic lesions are well known to begin in early life.[1-4] Initially, lesions are seen as fatty streaks in the aorta of persons as young as age 3 years.[1] Similar lesions occur in coronary arteries with fibrotic and elevated lesions developing during the second decade of life. These progress in early adulthood and set the stage for clinical disease later. Advanced lesions seen at autopsy of young soldiers killed in the Korean and Vietnamese wars clearly indicated that coronary artery lesions present in men in the second and third decades of life are abnormally pervasive in our society.[2,3]

Although the clinical manifestations of cardiovascular disease and coronary heart disease appear only later in life, epidemiologic studies in adults have identified risk factors, i.e., serum lipids and lipoproteins, blood pressure levels and smoking, that predict clinical disease. Autopsy studies in adults have been able to relate risk factors to postmortem lesions,[4] but only recently have the relations of antemortem risk factor measurements to the extent of vascular disease in childhood been reported.[5,6] Observations from a multicenter study of young adults are also showing a strong relation of risk factors, like smoking and lipoproteins, to anatomic disease.[7] Further observations from the Bogalusa Heart Study, especially on coronary vessels, are now presented to provide credibility for examining young persons for clinical risk factors and the initiation of preventive cardiology in early life.

METHODS

Population: The Bogalusa Heart Study is a long-term epidemiologic study of risk factors for cardiovascular disease from birth through the age of 31 years in a biracial (65% white/35% black) population.[8,9] Six cross-sectional surveys, each having 80 to 90% participation and including over 3,500 children, were conducted since 1973 (The general population is approximately 22,000 persons.) The first survey examined 5- to 14-year-old subjects in 1973, with subsequent examinations of school-age children extended through the 12th grade to ages 17 to 18 years. In addition, surveys after high school have been conducted since 1976 for reexamination of previous school-age participants. To date, data on approximately 12,000 persons have been collected. Some risk factor information has also been obtained during pilot studies conducted in Franklinton, Louisiana, a nearby community. The risk factors studied in-

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TABLE I Race, Sex and Age Distribution of Autopsy Studies on Children and Young Adults: The Bogalusa Heart Study

Age at Death (year)	Number (% of race-sex group)				
	White		Black		
	Male	Female	Male	Female	Total
Subjects with Antecedent Risk Factor Determinations (n = 66)					
3–8	4 (11)	1 (9)	0	0	5
9–14	1 (3)	2 (18)	1 (7)	1 (20)	5
15–20	20 (57)	3 (27)	8 (53)	2 (40)	33
21–26*	9 (26)	4 (36)	5 (33)	1 (20)	19
27–30*	1 (3)	1 (9)	1 (7)	1 (20)	4
Total	35	11	15	5	66
Cases Without Antecedent Risk Factor Determinations (n = 79)					
3–8	0	2 (14)	1 (6)	3 (20)	6
9–14	1 (3)	0	2 (11)	0	3
15–20	14 (44)	5 (36)	3 (17)	1 (7)	23
21–26*	13 (41)	6 (43)	9 (50)	11 (73)	39
27–30*	4 (13)	1 (7)	3 (17)	0	8
Total	32	14	18	15	79

*These older ages were added in 1982, 4 years after the autopsy study began to coexist with aging of subjects in the Bogalusa Heart Study.

clude levels of serum total cholesterol, serum triglycerides, very low density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure, measures of body size and obesity, as well as lifestyles including cigarette smoking, alcohol consumption, oral contraceptive use and dietary intake. In addition, a brief family history was obtained. Detailed protocols for collection of observations have been followed and the methods described earlier.[8,9]

A local information system was developed in 1978 to obtain families' or coroner's consent to conduct an autopsy on any resident of Washington or an adjacent parish (county) who died between ages of 3 and 31 years. (Older ages have been included as the study population aged.) Autopsies are conducted in local funeral homes or hospital morgues in adjacent communities, and selected tissues (including heart and coronary arteries, aorta, kidneys, adrenal glands and blood) are sent to the Department of Pathology and to the Core Lipid Laboratory at Louisiana State University Medical Center in New Orleans. As of September 1989, autopsy specimens were collected on 150 cases representing >60% of all known, eligible deaths in Washington Parish (county). The age, race and sex distributions of the subjects with and without clinical risk factor determinations are listed in Table I. Estimates of body weight are recorded at autopsy. Hearts are fixed in formalin and weighed to the nearest gram.

Most deaths were accidents, homicides or suicides; only about 10% were related to renal, neoplastic and infectious diseases. Of the 150 deceased subjects, 66 had been previously examined as part of the Bogalusa Heart Study. Forty-one subjects were examined more than once. Eleven were examined twice, 2 examined 3 times, 9 examined 4 times, 16 examined 5 times, 1 examined 6 times, 1 examined 7 times, and 1 examined 8 times.

Cardiovascular risk factor characterization: Risk factor screening procedures for obtaining anthropometric, blood pressure, and serum lipid and lipoprotein measurements have been reported earlier.[8,9] Height was measured to the nearest 0.1 cm, weight to the nearest 0.1 kg, and triceps and subscapular thickness to the nearest 1 mm. The ponderal index (weight/height^3) was used as a measure of obesity.

Replicate blood pressures were measured in the right arm, with a subject in a relaxed sitting position. The average of 6 measurements (3 taken by each of 2 examiners) with a mercury sphygmomanometer was used in all analyses. A fourth Korotkoff phase was considered the diastolic blood pressure. A smoking history was obtained by questionnaire. Fasting venous blood was collected and shipped in cold packs to New Orleans. Serum total cholesterol, triglycerides and lipoprotein cholesterol were measured in a standardized laboratory by procedures that have been described in detail previously.[10]

Procedure for evaluating atherosclerotic lesions: Aortas and coronary arteries were opened longitudinally, stained with Sudan IV for lipid deposition, and intermixed with specimens from other research projects for grading procedures. The vessels were graded visually for the extent of the intimal surface involvement with fatty streaks, fibrous plaques, or complicated lesions by procedures developed in the International Atherosclerosis Project and currently being used by the Department of Pathology at Louisiana State University Medical Center.[4,5] Three pathologists evaluated the vessels independently and a mean grade was used. Aortas were available in 134 subjects, and coronary arteries in 119 subjects. Several specimens were unavailable because of gunshot or other traumatic causes of death.

Statistical analyses: Analyses of the observations included only 145 subjects dying from accidents, homicides or suicides. Four of the 150 cases were excluded from analyses because of unusual heart weights (560 to 1,560 g), 1 because of an usually severe coronary involvement with atherosclerotic lesions (42% of intimal surface). Sixty-six of these 145 autopsy subjects had previously measured risk factor levels. Of the 66 persons with antemortem risk factor levels, aortas were available in 62, and coronary arteries in 57. Study- and age-specific Z scores were used to eliminate the effects of age and laboratory drift on risk factor levels. The Z-score calculations were then reconverted into original units, with 14-year-old children from the first survey as a reference population. For the 41 persons with >1 set of risk factor measurements, adjusted levels were averaged over all examinations.

Associations between lesions in the aorta and lesions in the coronary arteries were examined by Spearman correlations; this nonparametric analysis is based on ranks and is therefore not influenced by skewed distributions. Spearman correlations were also used to investigate the association of risk factor levels with fatty streak lesions. Associations for VLDL cholesterol and triglycerides excluded any antecedent nonfasting measurements.

Linear regression analyses were used to examine the relation of percent fatty streak or fibrous plaque involvement of vessels with age at death. Analysis of variance techniques were used to test for significant differences in mean percent of fatty streak involvement of aorta and coronary vessels among LDL and HDL cholesterol quartiles. Wilcoxon rank-sum tests were used to examine differences in risk factor levels between subjects with and without fibrous plaque. All statistical tests were 2-sided. The Statistical Analysis System was used for all analyses.[11]

RESULTS

Description of study population: The ages at death ranged from 6 to 30 years (mean 20), with three-fourths occurring between the ages of 17 and 27 years. Ages at last risk factor examination ranged between 3 and 24 years (mean 12). The longest interval between the last examination and death was 16 years. The shortest was 3 weeks. Eleven subjects were smokers at the time of risk factor observation.

As in earlier reports,[5,6] male subjects were overrepresented in the study population compared with the reference population, whereas black female subjects were especially underrepresented. The mean levels of risk factors in the study group were similar to comparable persons in the general population after covariance adjustment for race and sex.

Intimal surface involvement of aorta and coronary arteries: Distributions of intimal surface involvement by atherosclerotic lesions for male subjects by age and race are shown for aorta in Figure 1 and for coronary vessels in Figure 2.

The intimal surface involvement with aorta fatty streaks was extensive (range 0 to 71%), and greater than that noted for fibrous plaques. Male subjects tended to have more involvement and at a younger age. Blacks had approximately 1½ as much intimal surface involvement with aorta fatty streaks as did whites (32 vs 20%, p <0.001), as demonstrated in an earlier study.[6] This racial difference was seen in both sexes and observed in various locations in the aorta. Fatty streaks were also present in coronary arteries in most cases, with the intimal surface visibly covered by lesions at an average of 3.0% (range 0 to 22%), 42% in the 1 case excluded.

Fibrous plaques were observed in both aorta (23%) and coronary artery (44%) specimens. However, the surface involved by gross examination was not extensive (range 0.1 to 12% surface in the aorta and from 0.1 to 24% in the coronary arteries). It is apparent that more male than female subjects had both fatty streak and fibrous plaque lesions present in the intimal surface, and the distribution was relatively more extensive in male

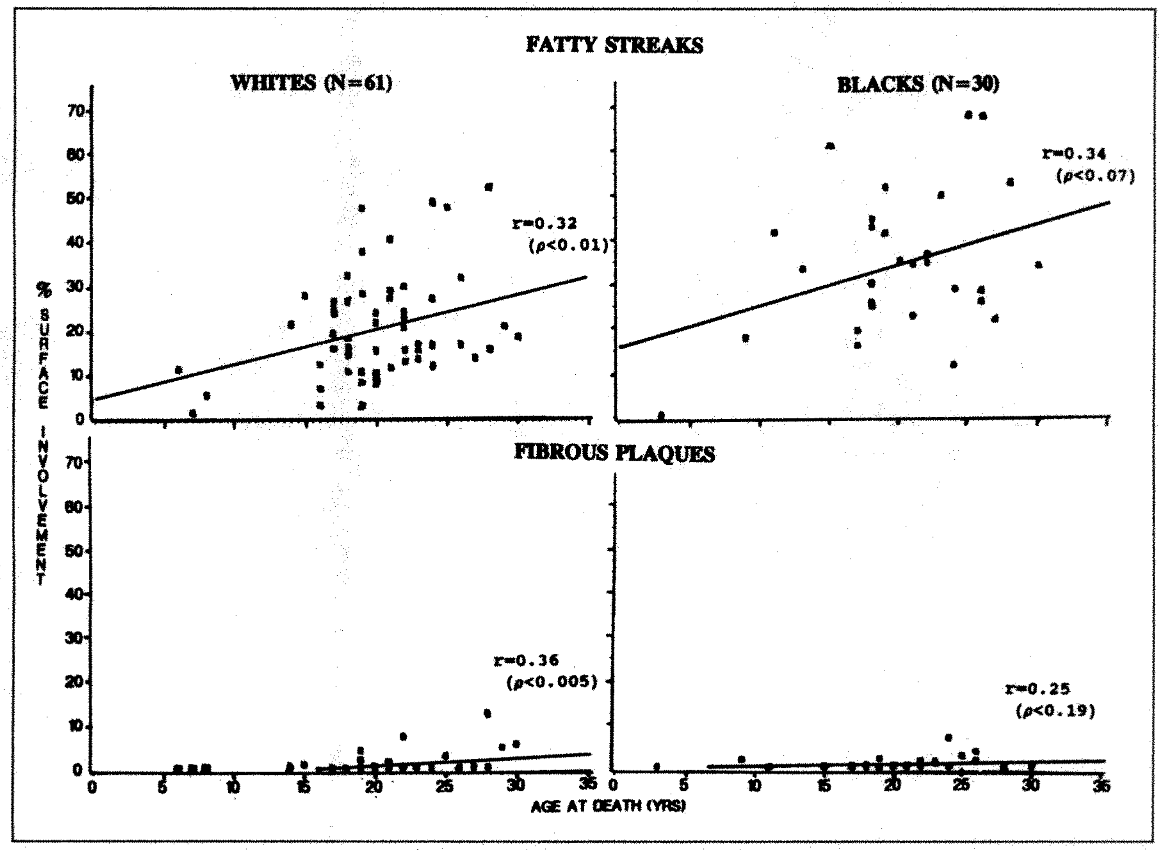

FIGURE 1. Distribution of atherosclerotic lesions in aortas of male children and young adults autopsied in the Bogalusa Heart Study documenting an increased surface with fatty streaks in blacks. Comparable observations in female patients showed fatty streaks in whites (r = 0.58, p <0.003) and in blacks (r = 0.67, p <0.002), and fibrous plaques in white females (r = 0.47, p <0.05) and in black females (r = 0.41, p <0.08).

TABLE II Persons Selected Based on Presence of Coronary Fibrous Plaque Lesions (occurrence of lesions by age, race and sex)

Whites										Blacks									
Males (n = 56)*					Females (n = 21)					Males (n = 26)					Females (n = 16)				
	Percent Surface Involvement					Percent Surface Involvement					Percent Surface Involvement					Percent Surface Involvement			
Age (yr)	FS	FP	Ca	Comp.	Age (yr)	FS	FP	Ca	Comp.	Age (yr)	FS	FP	Ca	Comp.	Age (yr)	FS	FP	Ca	Comp.
17	2.31	0.44	0	0	20	0.69	0.53	0	0	17	3.41	0.22	0	0	19	1.21	0.33	0	0
17	0.43	0.57	0	0	22	13.89	14.37	0	0.62	19	1.09	1.13	0	0	21	7.05	5.47	0	0
17	6.11	0.39	0	0	22	18.58	2.8	0	0	21	1.17	0.54	0	0.28	22	0.55	1.66	0	0.11
17	1.46	0.08	0	0	23	4.13	2.08	0	0	22	3.84	2.14	0	0	22	0.88	0.67	0	0
18	4.26	0.83	0	0	27	0.99	0.17	0	0	22	10.99	24.39	0.62	0	22	16.67	0.35	0	0
19	10.63	2.73	0	0						23	0.55	1.1	0	0	22	5.47	0.27	0	0
19	0.67	0.78	0	0						24	5.58	2.16	0	0	25	4.12	0.84	0	0.03
19	1.69	1.63	0	0						25	10.74	6.12	0	0	25	1.70	0.40	0	0
20	7.85	0.89	0	0						26	0.44	0.33	0	0					
20	2.04	0.28	0	0						26	2.92	0.61	0	0					
20	1.16	0.17	0	0						26	16.57	10.28	0	0					
21	2.32	2.67	0	0						28	3.32	0.33	0	1.00					
21	2.87	0.44	0	0															
22	1.41	0.24	0	0															
22	6.42	4.33	0	0															
22	3.52	0.33	0	0															
22	5.31	5.11	0.44	0															
23	0.68	1.43	0	0															
23	0.07	2.25	0	0															
24	2.98	0.67	0	0															
24	8.87	7.12	0	0.07															
24	0.61	0.39	0	0															
25	14.43	13.80	0	0.88															
26	6.99	19.00	0.17	0.17															
26	2.20	3.37	0	1.64															
27	0.89	1.22	0	0															
28	3.47	5.19	0	0															
30	1.28	2.27	0	0															

*n = total number of autopsy cases with presence or absence of fibrous plaques based on gross observations.
Ca = calcification; Comp. = complicated or ulcerated; FP = fibrous plaques; FS = fatty streaks.

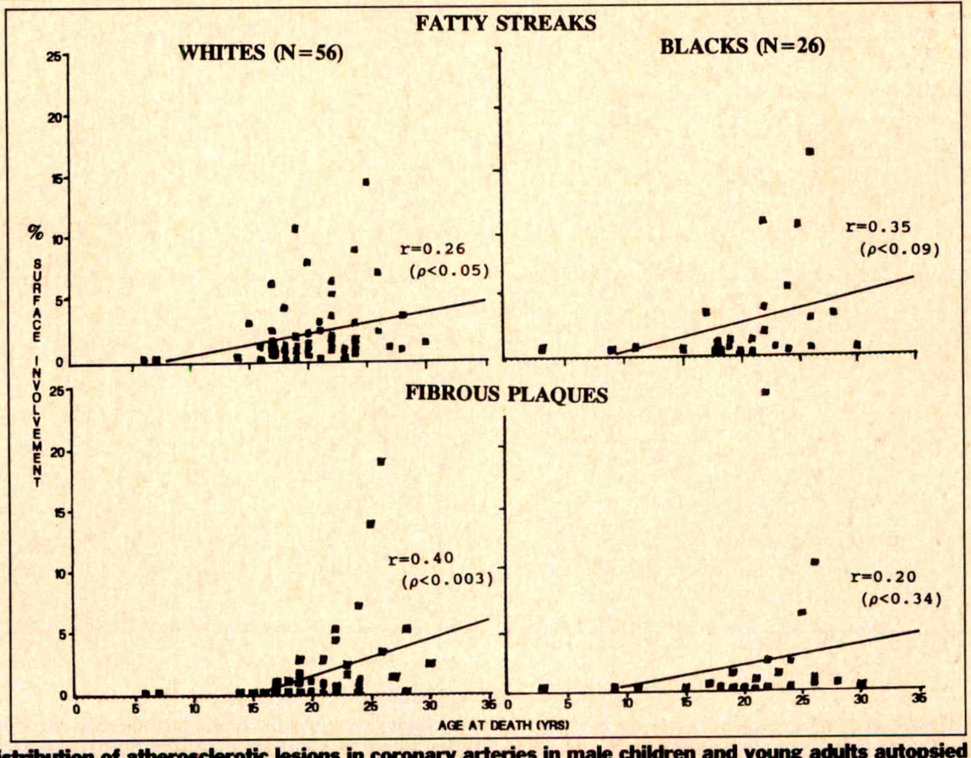

FIGURE 2. Distribution of atherosclerotic lesions in coronary arteries in male children and young adults autopsied in the Bogalusa Heart Study documenting an increased surface involvement with fibrous plaques in whites. Comparable observations on females showed fatty streaks in white females (r = 0.32, p <0.16) and in black females (r = 0.47, p <0.07), and fibrous plaques in white females (r = 0.20, p <0.38) and in black females (r = 0.15, p <0.57).

TABLE III Association* Between Percent of Atherosclerotic Lesions (fatty streaks and fibrous plaques) in the Aorta and Coronary Arteries: The Bogalusa Heart Study

	All Children and Young Adults (n = 116)	White Males (n = 54)	Black Males (n = 25)	White Females (n = 21)	Black Females (n = 16)
Fatty streaks aorta vs fibrous plaques aorta	0.17†	0.08 (NS)	0.23 (NS)	0.20 (NS)	−0.04 (NS)
Fatty streaks aorta vs fatty streaks coronary arteries	0.45‖	0.47§	0.39†	0.60‡	0.36 (NS)
Fibrous plaques aorta vs fibrous plaques coronary arteries	0.31§	0.27‡	0.71†	0.44†	−0.26 (NS)
Fatty streaks aorta vs fatty streaks + fibrous plaques coronary arteries	0.46‖	0.42§	0.40†	0.62§	0.43 (NS)
Fatty streaks coronary arteries vs fibrous plaques coronary arteries	0.62‖	0.69‖	0.79‖	0.42†	0.30 (NS)

*Values are Spearman rank-order correlation coefficients corrected for ties (p value).
p values = †0.05; ‡0.001; §0.001; ‖0.0001.
NS = not significant.

subjects. The observations suggest that lesions appear earlier and become more advanced in men, especially with coronary artery fibrous plaques, with fewer lesions occurring in white women (Table II). Lesions are also more extensive in the proximal portion of the coronary vessels, especially the left anterior descending coronary (data not shown). Some subjects were noted to have calcified and complicated lesions with small ulcerations indicative of more advanced disease.

The correlation of atherosclerotic lesions, fatty streaks and fibrous plaques in the aorta with those in coronary vessels is only moderate (Table III). However, the correlation of fatty streaks with raised fibrous plaque lesions was much greater in the coronary vessels than in the aortic vessels. In general, the correlations were greater in male than in female subjects.

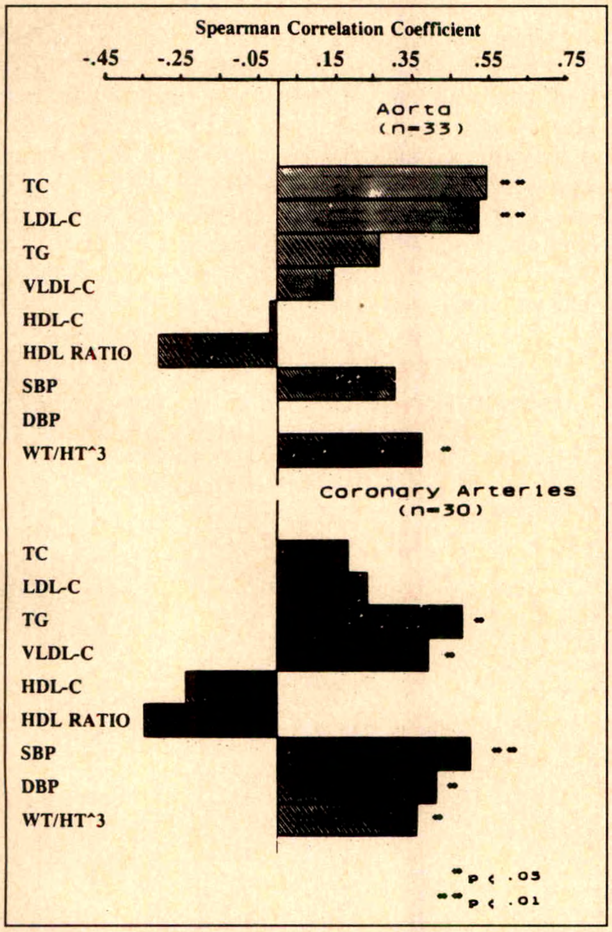

FIGURE 3. Association between fatty streak involvement and risk factor levels in white male subjects. A high correlation ($r = 0.54$, $p < 0.01$) with total cholesterol and low-density lipoprotein cholesterol (LDL-C) in serum was noted for lesions in the aorta, and an inverse trend for was noted for high-density lipoprotein cholesterol (HDL-C) ratio. A high correlation was also noted for systolic blood pressure (SBP). In contrast significant correlation was seen in the coronary vessels with very low density cholesterol (VLDL-C), triglycerides (TG) and diastolic blood pressure (DBP) ($r = 0.47$, $p < 0.05$). Both aorta and coronary arteries correlated with ponderal index (WT/HT_3 [weight/height^3]).

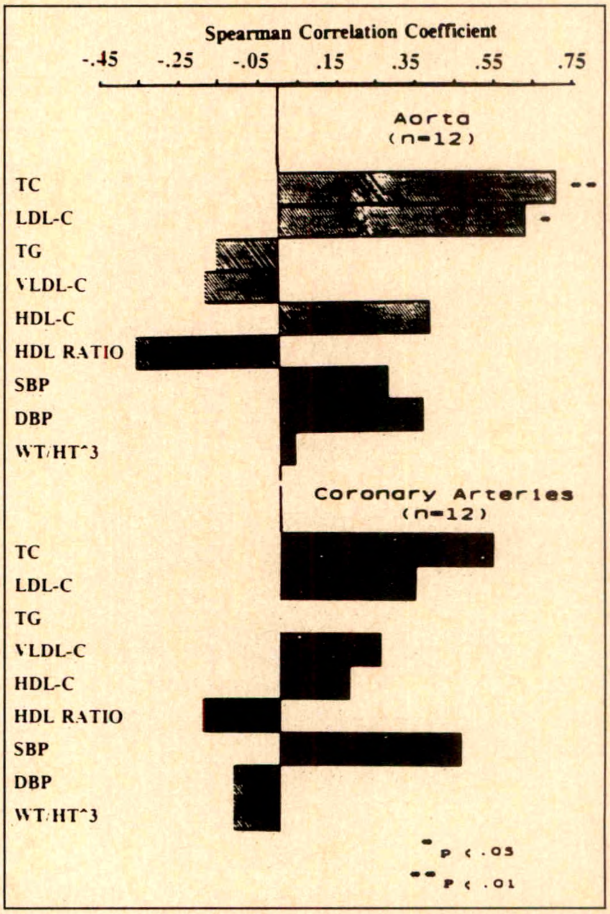

FIGURE 4. Association between fatty streak involvement and risk factor levels in black male subjects. The only significant correlations were with total cholesterol ($r = 0.74$, $p < 0.01$) and low-density lipoprotein cholesterol (LDL-C) ($r = 0.64$, $p < 0.05$). Abbreviations as in Figure 3.

TABLE IV Mean Age-Adjusted Risk Factor Levels by Tertiles of Fatty Streaks: The Bogalusa Heart Study

Risk Factor*	Tertile of Lesions			p Value Significance
	Low	Middle	High	
Aorta (n = 62)				
Total cholesterol (mg/dl)	131	144	172	p <0.0001
Triglycerides (mg/dl)	72	73	83	NS
Lipoprotein cholesterol (mg/dl)				
LDL	65	74	97	p <0.0001
HDL	58	58	60	NS
VLDL	9	11	13	NS
HDL ratio	0.80	0.80	0.65	NS
Blood pressure (mm Hg)				
Systolic	103	107	107	NS
Diastolic	67	66	66	NS
Ponderal index (kg/m^3)	11.8	12.2	13.0	NS
Coronary Artery (n = 57)				
Total cholesterol (mg/dl)	143	149	159	NS
Triglycerides (mg/dl)	68	74	89	NS
Lipoprotein cholesterol (mg/dl)				
LDL	72	78	90	p <0.05
HDL	61	61	55	NS
VLDL	9	9	14	p <0.05
HDL ratio	0.82	0.81	0.61	NS
Blood pressure (mm Hg)				
Systolic	104	103	113	p <0.001
Diastolic	66	66	69	NS
Ponderal index (kg/m^3)	11.8	12.4	13.3	NS

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant; VLDL = very low density lipoprotein.

Relations between cardiovascular disease risk factors and lesions: The association of fatty streaks with cardiovascular risk factors for all decedents with antemortem risk factor data for both aorta and coronary vessels (data not shown) indicate fatty streaks are strongly associated with serum total cholesterol and LDL cholesterol (r = 0.63; p <0.001) (as we have previously reported[5,6]) and inversely related to the ratio of HDL cholesterol/LDL cholesterol and VLDL cholesterol. Trends for relation with ponderal index, VLDL cholesterol and blood pressure are found. Involvement in the aorta was not related significantly to smoking, although mean surface involvement with fatty streaks was greater for white male subjects who were smokers. Certain differences were noted in the coronary arteries, with significant correlations occurring with VLDL cholesterol and systolic blood pressure; other risk factors showed trends in the expected directions.

In Figures 3 and 4, the association of cardiovascular risk factors with fatty streaks in the coronary vessels is shown for white and black male subjects, respectively. In white males, the associations of total cholesterol (r = 0.54, p <0.01), LDL cholesterol (0.53; p <0.01) and ponderal index (r = 0.38; p <0.05) with fatty streaks were noted in the aorta. In the coronary arteries significant correlations were noted with fatty streaks and serum triglycerides (r = 0.48; p <0.05), VLDL (r = 0.36; p <0.05), systolic (r = 0.54; p <0.05) and diastolic (r = 0.47; p <0.01) blood pressure levels, and with the ponderal index (r = 0.37; p <0.05); a nonsignificant trend was seen to relate inversely with HDL

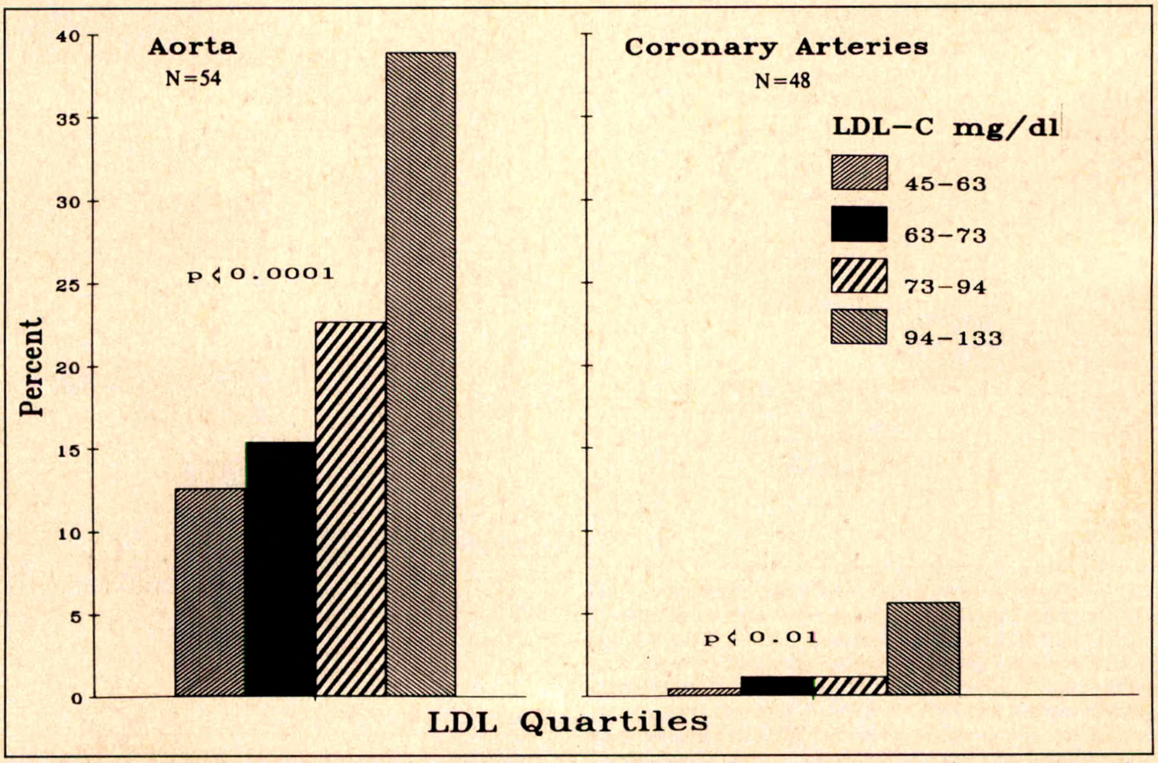

FIGURE 5. Fatty streak intimal surface involvement of aorta and coronary vessels according to low-density lipoprotein cholesterol (LDL-C) quartiles in children and young adults autopsied in the Bogalusa Heart Study. Increasing low-density lipoprotein cholesterol levels are significantly related to increasing amounts of aorta and coronary vessel fatty streaks.

cholesterol and an associated ratio ($r = 0.30$). The relation of serum total cholesterol and LDL cholesterol with fatty streak lesions was not as strong in the coronary arteries as in the aorta (Figure 5); the multiple risk factor relation noted with the coronary lesions were less evident in the aorta. Black male subjects had high correlations ($r = 0.74$; $p < 0.01$) of total cholesterol and LDL cholesterol ($r = 0.64$; $p < 0.01$) with aorta fatty streaks; no such significant correlations were noted for any of the cardiovascular risk factor variables in the coronary lesions.

In persons aged >20 years with fibrous plaque involvement of the coronary vessels, the observations suggest a greater involvement in white males who are smokers. Subjects with fibrous plaques tended to be older at death (range 17 to 30 years, mean 23).

In females, the limited number of observations do not allow detailed correlation analyses.

Risk factor levels stratified by tertiles of fatty streaks in the aorta or coronary vessels are listed in Table IV. These stratifications show the influence of serum total cholesterol and LDL cholesterol in the aorta, but more risk factors and multirisk factor relations in the coronary vessels.

DISCUSSION

Autopsy studies in the Bogalusa Heart Study give credibility to clinical risk factor examination of young persons, and the beginning of risk factor control early in life. Extensive observations on large numbers of persons by the multicenter Pathobiologic Determinants of Atherosclerosis in Youth study also emphasize this need.[7] Current studies show the importance of risk factor measurements in young persons by linking their clinical observations with lesions that potentially can progress to symptomatic disease in later life. Further research is needed to elucidate the high association of serum total cholesterol and LDL cholesterol with fatty streaks in the aorta and, in contrast, the multiple risk factor relations in the coronary vessels. It is of considerable importance that the involvement of the coronary arteries is associated with multiple risk factors. This relation in the coronary vessels of young persons is somewhat akin to the concept of a multiplicative effect of risk factors that lead to end-stage coronary heart disease as shown in the Framingham Study.[12] Further, the very obvious differences of involvement in male versus female subjects is borne out by relevant study of clinical disease and morbidity. Interestingly, relatively fewer fibrous plaque lesions were noted in white females (Table II) than in black females in whom clustering of risk factors, hyperinsulinemia, obesity, high blood pressure and lipids were found.[9] Older persons with a long smoking history and clinical occurrence of hypertension and renal disease had much more extensive coronary and vascular lesions. One such patient with renal disease had marked cardiomegaly (1,560 g) and severe coronary artery disease, 2% fatty streaks and 43% fibrous plaques.

One should note the positive relation of VLDL cholesterol and the trend for an inverse relation of HDL cholesterol with lesions in the coronary arteries in white males. Selectively, white males had a marked decrease of HDL cholesterol during puberty and an earlier increase in LDL cholesterol in young adulthood.[13,14] Other observations in the Bogalusa Heart Study[15] note even mild obesity to be related to higher levels of insulin, blood pressure, VLDL and LDL cholesterol and lower HDL cholesterol, a cluster of findings very often found in adults.[16,17] As is apparent in adult clinical disease, namely obesity, diabetes and coronary artery disease, an influence of central obesity on risk factors is also seen in children. Insulin, indicated to act as a growth factor, has been implicated in the development of atherosclerotic lesions[18] and in the development of hypertension.[19,20] From these autopsy studies, the cluster of parameters related to carbohydrate-lipid metabolism and obesity seems to influence the severity of atherosclerotic disease in its early stages.

The divergent nature and extent of vascular disease in different locations, e.g., aorta versus coronary vessels, are of interest. The low correlation of fatty streak and raised lesions in the 2 different sites is not explained, but has been noted earlier.[21] The correlation of both systolic and diastolic blood pressure to coronary lesions is noteworthy. Certainly, the importance of hemodynamic factors varies in the different vascular sites, and hemodynamic stress is known to play a major role in the severity and progressive nature of disease at the different sites.[22] The anatomic structural differences, the size of the vessels, and the functional hemodynamic load all likely enter into determining the severity of the disease process. These factors may in part account for the sex and racial differences in the extent of diseases noted, especially for coronary vessels.

Fatty streak lesions of the aorta seem to be reversible, because these are found in populations with a low incidence of coronary artery disease[23]; thus, debate remains as to whether it is a precursor of fibrous plaques. McGill[24] considers the fatty streak lesions that occur in the coronary arteries, in contrast to those in the aorta, as the precursor of the progressive and elevated fibrous plaque lesions in coronary arteries. The highly significant correlation of fatty streaks to fibrous plaques in the coronary arteries (Table III) in contrast to the aorta support this concept. The similarity of fatty streaks being located where fibrous plaques appear, the later onset of lesions in the coronary arteries, and the greater involvement of the coronary arteries with a relatively greater portion of fibrous plaques are consistent with more extensive disease evolving from fatty streaks in coronary vessels. The high pressure relative to vessel size may also be a factor in the progressive nature of disease occurring in the coronary arteries. Furthermore, the propensity for thrombotic disease to contribute to the progressive nature of coronary lesions more so than in the aorta may also be a factor.[25] Interestingly, some of the coronary lesions already demonstrated calcification and ulceration. The close association of multiple risk factors with lesions in the coronary arteries, especially in young white males, is in concert with the experience of clinical and epidemiologic studies of adult disease.

The location of early involvement of the coronary arteries occurs primarily in the left anterior descending artery. Although lesions occur in distal sites and in the right coronary system, lesions appear first in the proximal coronary vessels and become more advanced in those sites. Changes noted by histologic and electron microscopic studies even show macrophage infiltration into coronary vessels in early infancy.[26] As may be expected, the development of intracellular lipid deposition begins very early. The development of foam cells from the monocyte-macrophage uptake of modified LDL and other apolipoprotein-B-containing lipoproteins including lipoprotein (a),[27-29] underlies the increased synthesis of intracellular cholesteryl ester as the hallmark of early vascular lipid deposition. It is in this initial phase of intracellular lipid deposition, before the more advanced collagen capping encasing the lesion, that regression can take place. It could then be presumed that control of risk factors in childhood might delay or attenuate the progression of atherosclerotic disease more effectively. This may be the important message from the autopsy studies.

The relation of smoking to the development of coronary artery disease has to be emphasized.[30] Although limited information on subjects in this study does not allow evaluation of its significance, smoking appears to play a significant role in the development of lesions even in childhood. The need for emphasizing preventive cardiology and healthy lifestyles early in life is apparent.

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Efficacy of Enhanced External Counterpulsation in the Treatment of Angina Pectoris

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Eighteen patients with chronic angina despite surgical and medical therapy were treated with an improved system of enhanced external counterpulsation (EECP) (1 hour daily for a total of 36 hours). Patients underwent a baseline treadmill thallium-201 stress test. After EECP treatment, a thallium stress test was repeated for the same exercise duration. One week after treatment, patients also underwent a maximal stress test. All patients improved in anginal symptoms and generally decreased antianginal medications, with 16 obtaining complete relief from angina. Pre- and post-thallium stress testing performed for the same duration showed complete resolution of ischemic defects in 12 patients (67%), reduction in the area of ischemia in 2 (11%), and no change in 4 (22%). Thus, a decrease in myocardial ischemia was observed in 14 patients (78%; p <0.01). The exercise duration of maximal stress testing after EECP significantly improved from 8.14 ± 0.71 to 9.72 ± 0.77 minutes (p <0.005), although the double product did not change significantly. Analysis of these 2 tests in the subgroup of 14 patients with improvement in thallium studies showed significant increases in both exercise duration (8.58 ± 0.66 to 10.44 ± 0.59 minutes; p <0.001) and double product (21,827 ± 2,044 to 24,842 ± 1,707 mm Hg · beats/min; p <0.01).

The improvement in reperfusion defects and increase in exercise duration are reflections of improved perfusion to ischemic regions of the myocardium. EECP uses additional thigh balloons and sequenced balloon inflation, effecting a significant increase in diastolic augmentation over previously available methods. It appears to be a safe and effective therapy for selected patients with chronic angina.

(Am J Cardiol 1992;70:859–862)

External counterpulsation is a noninvasive treatment that has been demonstrated to improve survival in patients with cardiogenic shock after myocardial infarction[1] and to significantly reduce the mortality rate during the acute period after myocardial infarction.[2] Its physiologic effects are accomplished by increasing myocardial oxygen supply through increasing diastolic perfusion pressure and by reducing cardiac work load through decreasing left ventricular afterload. The efficacy of external counterpulsation in producing sustained benefits in patients with angina is unknown. The purpose of this study was to determine whether an improved system of enhanced external counterpulsation (EECP) alleviates the symptoms of patients with chronic angina and produces a sustained increase in the perfusion of the ischemic myocardium. Specifically, we assessed whether the hemodynamic changes produced by EECP would result in a sustained reduction of exertional ischemia and angina, and in an improved exercise tolerance. Thallium imaging was used to demonstrate exertional myocardial ischemia before treatment with EECP and to test for its presence after EECP. The change in functional status after EECP was assessed by symptom-limited stress testing.

METHODS

Patients: Patients with chronic, stable angina, despite medical and surgical therapy, and evidence of exertional ischemia by thallium-201 perfusion imaging were considered for inclusion in the study. Exclusion criteria were: clinical congestive heart failure, aortic insufficiency, myocardial infarction within the previous 3 months, significant ventricular ectopic activity or atrial fibrillation, nonischemic cardiomyopathy, severe occlusive peripheral vascular disease, recurrent deep vein thrombophlebitis, systemic hypertension (>180/110 mm Hg) and a bleeding diathesis.

Protocol: Patients were instructed to continue their usual medications. A baseline treadmill thallium-201 study was performed in all patients, using the standard Bruce protocol (test 1). The exercise was terminated because of symptoms such as chest pain, fatigue, dyspnea and claudication. The double product was calculated as the product of heart rate and systolic blood pressure obtained at peak exercise. Two minutes before cessation of exercise, 2.5 mCi of thallium-201 were injected intravenously and planar imaging was performed in the left anterior oblique, left lateral and anterior projections. Three hours later, redistribution images were obtained using the same projections. Reversible defects were considered indicative of myocardial ischemia, whereas fixed defects were considered to indicate myocardial infarction. Reinjection imaging was not performed. All thalli-

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um scans were interpreted by 2 experienced observers who did not know of the patient's participation in the study.

Patients were treated with EECP 1 hour daily for a total of 36 hours (Figure 1). All patients were monitored hemodynamically and clinically during EECP treatment. The diastolic augmentation pressures were progressively increased by increasing the external compression. The maximal external pressure used to maximize the diastolic/systolic pressure ratio (diastolic augmentation) was 280 mm Hg. Blood pressure waveforms were continuously monitored by finger plethysmography. Adjustments in anginal medications were determined by patients and their physicians during the course of the study. No other interventions were performed during the study.

After completing the course of EECP therapy, a thallium-201 stress test (with usual medications continued) was performed for the same exercise duration as at baseline to provide comparison of test results (test 2). Furthermore, ≤1 week after EECP treatment, a maximal stress test was performed to exercise tolerance (test 3).

Statistical analysis: Statistical analysis was performed using the chi-square test to examine differences in thallium perfusion images before and after EECP. Exercise parameters (exercise time, heart rate, blood pressure and double product) from both the thallium stress tests before and after EECP were compared using a paired, 2-tailed Student's *t* test (tests 1 and 2). Furthermore, the same exercise parameters from the thallium stress test before EECP (test 1) and the maximal stress test after EECP (test 3) were compared and evaluated for statistically significant differences, using a paired, 2-tailed Student's *t* test. The subgroup of patients with improvement in thallium scans after EECP were analyzed separately for changes in exercise duration and double product, using a paired, 2-tailed Student's *t* test. Statistical significance was achieved at the 5% level ($p < 0.05$).

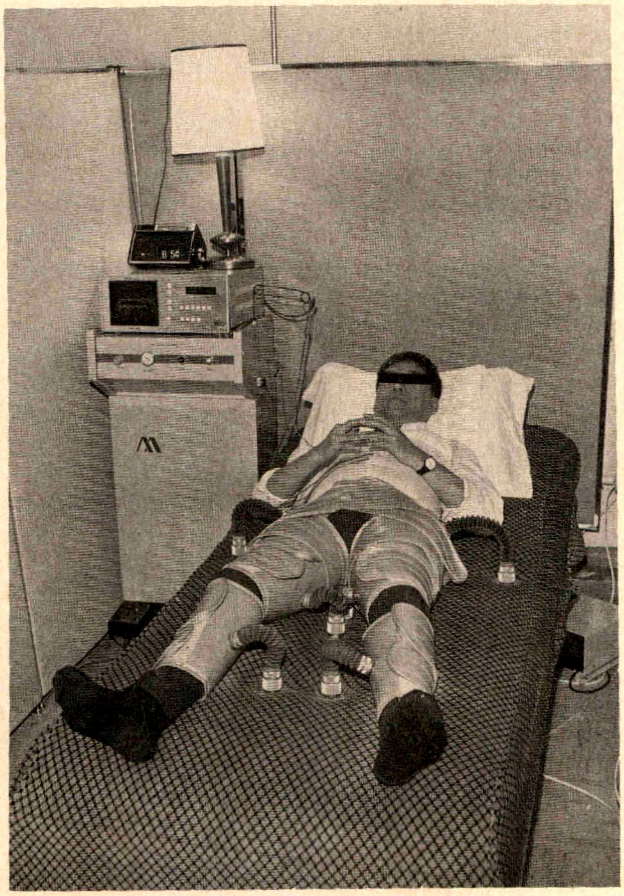

FIGURE 1. Enhanced external counterpulsation system consists of 3 sets of balloons wrapped around calves, and lower and upper thighs (including buttocks), which are inflated sequentially during diastole. Inflation is triggered by R wave. Control and display units are shown on *left*.

RESULTS

Seventeen men and 1 woman entered the study. All patients were receiving standard medical therapy with nitrates, β blockers or calcium antagonists. Before entry in the study, all patients experienced incapacitating angina despite medical therapy. Medication dosage and frequency remained unchanged or were adjusted downward in all patients during the study period. Eight patients underwent 19 prior attempts at revascularization by either angioplasty or bypass surgery. Seven patients had experienced a total of 14 myocardial infarctions and 2 patients had only abnormal thallium tests.

All 18 patients had substantial improvements in anginal symptoms after EECP; 16 had complete relief from angina during the usual activities of daily living. Thallium-201 stress testing (performed for the same exercise duration before and after EECP treatment) showed complete resolution of ischemic defects in 12 patients (67%), a decrease in the area of ischemia in 2 (11%), and no change in 4 (22%). Thus, 14 patients had a reduction in myocardial ischemia as assessed by thallium-201 imaging ($p < 0.01$). There were no significant differences in exercise duration and double product on the thallium stress tests before and after EECP (8.14 ± 0.71 vs 8.16 ± 0.76 minutes, and 22,062 ± 1,664 vs 20,532 ± 1,156 mm Hg · beats/min, respectively).

In comparing maximal stress test results after EECP with those before EECP (tests 1 and 3), there was a significant increase in exercise duration (8.14 ± 0.71 to 9.72 ± 0.77 minutes, $p < 0.005$; Figure 2) and no significant change in double product (22,062 ± 1,664 to 22,816 ± 1,653 mm Hg · beats/min; Figure 3).

Subgroup analysis of the 14 patients with improvement in thallium scans after EECP showed increases in both exercise duration (8.58 ± 0.66 to 10.44 ± 0.59 minutes, $p < 0.001$; Figure 4) and double product (21,827 ± 2,044 to 24,842 ± 1,707 mm Hg · beats/min, $p < 0.01$; Figure 5) in maximal stress testing after EECP.

DISCUSSION

In this study, EECP was performed by compressing the vascular beds within the muscles of the legs and thighs, including the buttocks, in a sequential manner, progressing from the calves to the lower and then upper thighs. The compression is accomplished by introducing air into 3 sets of balloons wrapped around the calves, and lower and upper thighs. The timing of the compression is controlled by the patient's electrocardiogram, so that increased blood flow and pressure will reach the coronary vessels during diastole at the time of lowest intramyocardial tension. Furthermore, the compression of the venous bed of the lower extremities increases venous return and cardiac output. The external pressure is then released during systole, causing systolic unloading and decreasing cardiac work load.

The 36-hour treatment course is performed for 1 hour daily over a period of approximately 7 weeks. The expectation that this will produce long-term benefit for patients with angina pectoris is based on the hypothesis

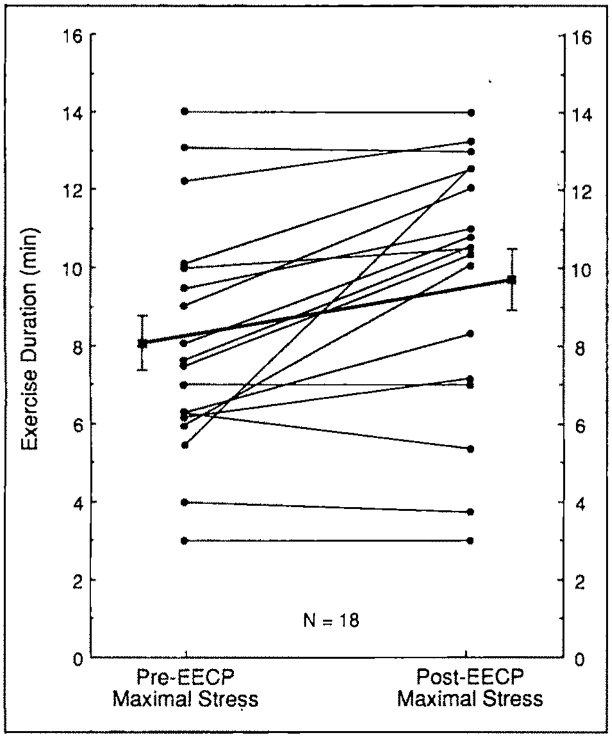

FIGURE 2. Maximal stress test duration before and after enhanced external counterpulsation (EECP). Mean durations ± 1 SEM are significantly different (p <0.005).

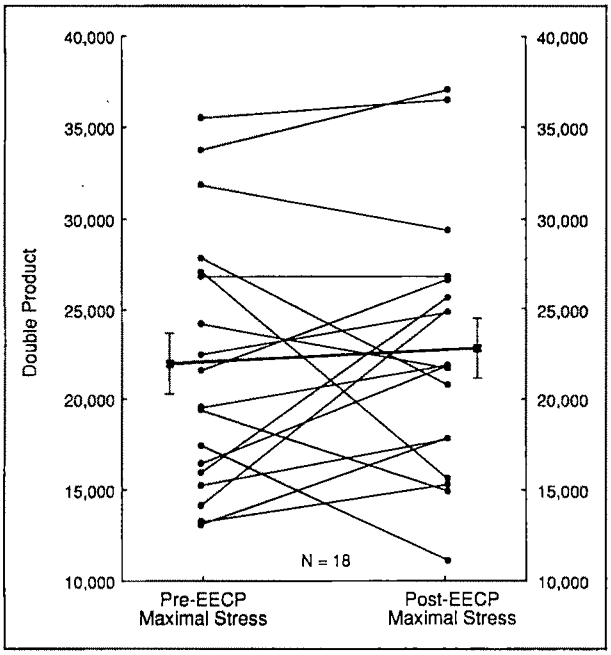

FIGURE 3. Double product (peak exercise heart rate × systolic pressure) before and after enhanced external counterpulsation (EECP). Mean double products ± 1 SEM are not significantly different.

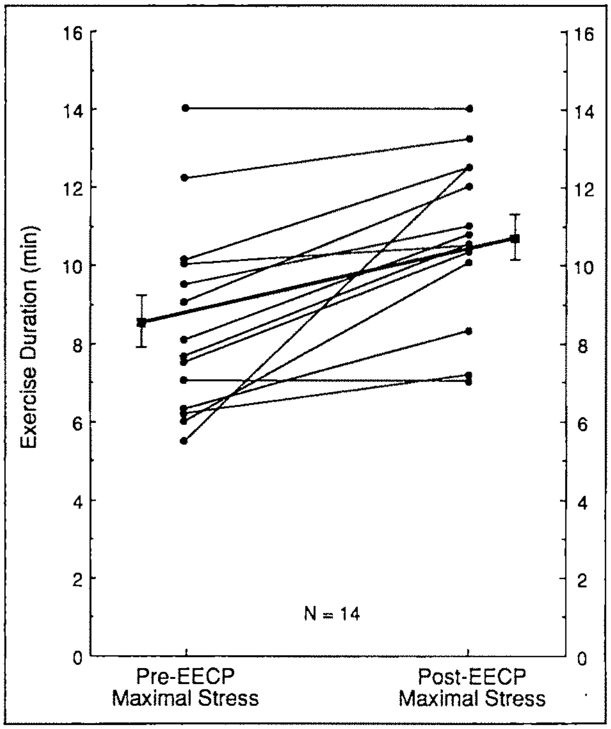

FIGURE 4. Maximal stress test duration before and after enhanced external counterpulsation (EECP) in subgroup of 14 patients with improved thallium perfusion. Mean durations ± 1 SEM are significantly different (p <0.001).

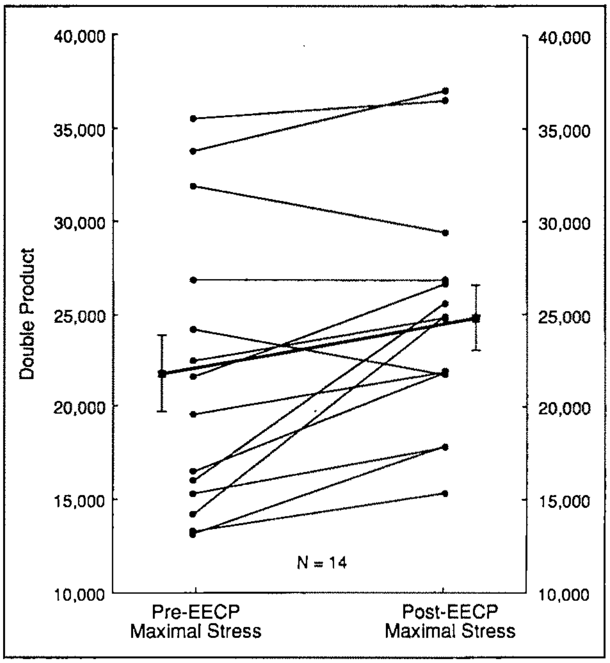

FIGURE 5. Double product before and after enhanced external counterpulsation (EECP) in subgroup of 14 patients with improvement in thallium reperfusion scans. Mean double products ± 1 SEM are significantly different (p <0.01).

that the repeated and pulsed increases in diastolic pressure enhance or stimulate the opening of collateral channels in the coronary vascular system, increasing perfusion of ischemic areas. Initial theoretical considerations suggest that ≥1 coronary vessel must be patent proximally to transmit the increased diastolic pressure and flow to the coronary vascular bed.

The use of counterpulsation in the treatment of patients with angina due to coronary artery disease was previously evaluated with mixed results.[3] However, a much less effective system for producing external counterpulsation was used in previous studies, in which compression was limited to the upper legs and lower thighs. Furthermore, water was used as the compressing medium.[2,4,5] The pioneering work of Zheng et al[6] created a greatly improved system for producing sequential external counterpulsation. This new system is capable of significantly augmenting the diastolic pressure by 46%, which is much greater than the previous system could accomplish.

In the present study, EECP was effective in improving exertional thallium perfusion defects in 14 of 18 patients with angina that was refractory to medical therapy. All 4 patients without improvement by thallium perfusion scintigraphy after EECP had either 3-vessel or diffuse coronary artery disease. The extensive nature of these patients' disease may have limited the effectiveness of EECP therapy.

The observed improvement in thallium perfusion after EECP for the same exercise duration was not caused by an alteration in the double product or heart rate. These determinants of myocardial oxygen demand did not significantly change in the thallium-201 stress tests after EECP. Because myocardial oxygen demand was unaltered by EECP treatment, the improvement in reperfusion defects is presumably a reflection of improved myocardial perfusion (increased supply), rather than a result of a peripheral training effect.

Patients with improved thallium scans demonstrated (not unexpectedly) an improvement in cardiac performance on maximal stress testing after EECP; they increased their exercise time by a mean of 1.46 minutes and simultaneously achieved an increase in double product by a mean of 3,015 mm Hg · beats/min.

The mechanism of the improvement remains speculative. Whereas some of the increase in exercise time could be due to a training effect, this could not explain the thallium finding. One possible explanation is that EECP may open or enhance the development of collateral channels. This may also explain the relative lack of efficacy in patients with severe and diffuse 3-vessel coronary artery disease. At least one open conduit may be necessary to enable transmission of the force and flow necessary to achieve this effect. Angiography and distal occluded pressures (not performed in our study patients) would be necessary to confirm collateral enhancement as a potential mechanism.

In a group of 200 patients with angina, Zheng et al[6] demonstrated prolonged symptomatic improvement in 97% of EECP-treated patients compared with 72% of medically treated control patients. Exercise tolerance was also found to be consistently improved. Similarly, Banas et al[3] found consistent improvement in symptoms in a small group of patients with frequent and disabling angina treated with external counterpulsation. Coronary angiography performed before and 4 to 8 weeks after counterpulsation in 11 patients showed increased vascularity in 5, equivocal changes in 4, and no visible changes in 2. The absence of visual macrocollaterals does not exclude improved coronary perfusion or rule out an improvement in myocardial function. Patency of ≥1 major epicardial vessel was necessary for the occurrence of clinical benefit in this study. Despite the potential benefits shown in these and other studies, external counterpulsation has been little used as a therapeutic modality in this country.[4]

In the present study, patients were used as their own controls. Whereas coronary artery disease is largely unpredictable in its course, regression would not be expected to occur over 6 to 7 weeks in this group of patients whose angina had been disabling or progressive over a period of months and years. The enrolled patients did not undergo any simultaneous therapy such as diet, lipid reduction, weight loss or smoking cessation. Antianginal medications were decreased in dosage or remained the same over the course of the study in all patients. The study cohort was predominantly male, and therefore definitive conclusions regarding efficacy in women should await future studies.

EECP was well-tolerated by all patients enrolled in the study. No patient withdrew after enrollment, and there were no complications of EECP therapy. Further studies are ongoing in this patient cohort to evaluate the long-term, sustained efficacy of EECP.

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Assessment of Left Ventricular Function in Kawasaki Disease by Dipyridamole-Loading Cineventriculography

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Dipyridamole-loading cineventriculography was performed to evaluate left ventricular (LV) function in 76 patients with Kawasaki disease. Forty-five of 76 patients underwent the procedure within 6 months from the onset of illness (group 1A, normal findings on coronary angiogram; group 1B, maximal diameter of coronary lesions <4 mm; group 1C, maximal diameter of coronary lesions >4 mm). Thirty-one of 76 patients underwent the procedure >6 months after onset (group 2A, coronary lesions improved to normal or <4 mm; group 2B, remaining coronary lesions >4 mm; group 2C, stenosis or obstruction of the coronary artery). Global LV ejection fraction increased in groups 1A, 1B and 2A after infusion of dipyridamole, but there was no significant change in groups 1C, 2B and 2C. In analyzing LV excursion, the pattern of LV wall motion with dipyridamole in groups 1B and 2A were similar to that in group 1A, but in 38% (5 of 13) of group 2A patients, abnormal regional LV wall motion after administration of dipyridamole was detected. Abnormal LV wall motion after dipyridamole infusion was detected in 42% (5 of 12) of group 1C patients, 38% (3 of 8 cases) of group 2B patients and 70% (7 of 10 cases) of group 2C patients.

In conclusion, analysis of LV wall motion with dipyridamole is useful in evaluating cardiac involvement in Kawasaki disease.

(Am J Cardiol 1992;70:863–868)

Mucocutaneous lymph node syndrome (Kawasaki disease), first described by Kawasaki in 1967,[1] is an acute febrile exanthematous disease of infants and children. The etiologic basis of this disease is unknown and the therapy for it has not been established. Kawasaki disease is regarded as myocarditis and panarteritis in all parts of the body, and the angiitis of coronary arteries is the major problem of this disease.[2,3] In the acute phase of illness, dilated coronary lesions are often detected. Most patients have subsequent regression of these lesions, but some lesions persist and coronary aneurysms often lead to coronary stenosis or obstructions.[4,5] Myocardial infarction and angina pectoris may occur in these patients. In some patients with myocarditis in the acute stage or coronary artery lesions, or both, left ventricular (LV) performance abnormalities were described.[6,7] Analysis of regional LV wall motion by cineventriculography or 2-dimensional echocardiography has been performed to evaluate LV function in Kawasaki disease.[8,9] We performed cineventriculography with intravenous administration of dipyridamole and analyzed regional LV wall motion to evaluate LV function in patients with a history of Kawasaki disease.

METHODS

Patient group: Seventy-six patients with Kawasaki disease (59 male and 17 female patients, ranging from 2 months to 8 years of age) were evaluated. The patients were categorized as follows. Forty-five of 76 patients underwent dipyridamole-loading cineventriculography within 6 months from the onset of illness (acute phase), and 31 of 76 patients did so >6 months from the onset of illness (chronic phase).

The patients in the acute phase of the illness were classified into 3 groups by coronary angiographic findings: group 1A (24 patients) had normal findings in the coronary angiogram; group 1B (9 patients) had dilated coronary lesions, maximal diameter <4 mm; and group 1C (12 patients) had dilated coronary lesions, maximal diameter >4 mm. No patient had stenosis or obstruction of the coronary artery during the acute phase.

Patients in the chronic phase had dilated coronary lesions in the acute stage of illness, and they were classified into 3 groups by coronary angiographic findings at this time: group 2A (13 patients) had coronary lesions that improved to normal or <4 mm; group 2B (8 patients) had remaining coronary artery lesions >4 mm; and group 2C (10 patients) had stenosis or obstruction of the coronary artery, or both.

Dipyridamole-loading cineventriculography: Cardiac catheterization was performed by way of the femor-

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al approach, and selective coronary angiography and left ventriculography were performed. Left ventriculography was achieved by injection of 1 ml/kg of contrast medium (Iopamidol) through the catheter for 2 seconds and recorded on 35 mm cine film at 50 frames/s. We obtained coronary cineangiograms and LV cineangiograms in biplane projections, a 30° right anterior oblique projection and a 60° left anterior oblique projection. After performing bilateral left ventriculography for control, dipyridamole, 0.3 mg/kg, was injected intravenously for 30 seconds. Heart rate and blood pressure were monitored before and after the procedure. Three minutes later, the second bilateral left ventriculography was performed.

Regional wall motion analysis (Figure 1): Two cine frames were selected from pairs before and after administration of dipyridamole at end-diastole and end-systole. The radial method was used for quantitative LV wall motion analysis in the right anterior and left anterior oblique views. In the right anterior oblique view, the long axis was defined as the line from the apex to the

TABLE I Heart Rate Responses to Dipyridamole

Group	Before Load (beats/min)	After Load (beats/min)	Percent Change (%)	p Value
1 A	113 ± 18	128 ± 16	13.5 ± 5.2	<0.01
1 B	103 ± 13	117 ± 11	14.4 ± 6.1	<0.01
1 C	107 ± 19	121 ± 16	13.4 ± 5.9	<0.01
2 A	91 ± 13	108 ± 15	19.1 ± 9.4	<0.01
2 B	83 ± 14	102 ± 14	23.5 ± 10.7	<0.01
2 C	87 ± 12	104 ± 13	20.7 ± 8.5	<0.01

Values are mean ± SD.

TABLE II Blood Pressure Responses to Dipyridamole

Group	Before Load (mm Hg)	After Load (mm Hg)	Percent Change (%)	p Value
1 A				
(S)	97 ± 10	87 ± 7	9.6 ± 4.8	<0.01
(D)	55 ± 8	45 ± 7	18.3 ± 7.5	<0.01
1 B				
(S)	98 ± 10	90 ± 9	8.6 ± 5.9	<0.01
(D)	60 ± 11	48 ± 8	18.6 ± 11.7	<0.01
1 C				
(S)	103 ± 11	92 ± 13	9.3 ± 4.8	<0.01
(D)	63 ± 13	50 ± 11	18.2 ± 10.2	<0.01
2 A				
(S)	102 ± 9	93 ± 11	8.6 ± 5.1	<0.01
(D)	63 ± 9	53 ± 9	16.1 ± 9.3	<0.01
2 B				
(S)	106 ± 9	99 ± 9	7.5 ± 4.0	<0.01
(D)	69 ± 8	59 ± 12	15.4 ± 9.6	<0.01
2 C				
(S)	105 ± 12	95 ± 11	8.7 ± 8.0	<0.01
(D)	66 ± 12	56 ± 8	13.8 ± 11.6	<0.01

Values are mean ± SD.
(D) = diastolic pressure; (S) = systolic pressure.

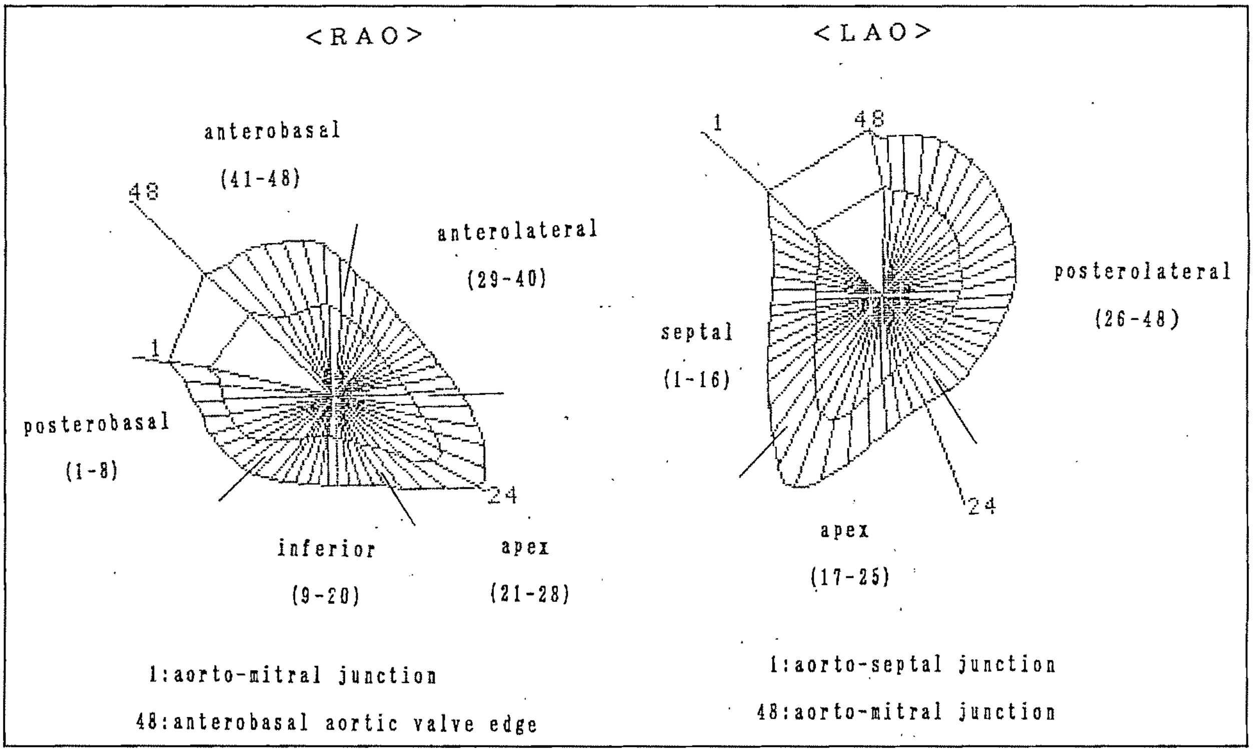

FIGURE 1. Radial method. Left ventricular silhouettes from cineangiogram were superimposed at end-diastole and end-systole. The radial length was measured at each phase and percent systolic radial shortening (excursion) was calculated from radius 1 through 48. The left ventricle was subdivided into 5 segments in the right anterior oblique (RAO) view and 3 segments in the left anterior oblique (LAO) view. Excursion = (EDRL − ESRL)/EDRL × 100%, where EDRL = end-diastolic radial length, and ESRL = end-systolic radial length.

midpoint of the aortic valve. The end-diastolic and end-systolic frames were superimposed along the long axis and its center. In the left anterior oblique view, transformation and superimposition were performed on the end-diastolic center of gravity and the connecting line between the center of gravity and the aortic-septal junction.

Forty-eight lines (radii) were drawn from the center to the endocardial margin, excluding the aortic valve portion. LV wall motion was evaluated by these 48 radii, which corresponded to the ventricular muscular portion. Radial length at end-diastole and at end-systole were measured, and percent systolic radial shortening

TABLE III Ejection Fraction Responses to Dipyridamole

Group	Before Load (%)	After Load (%)	Percent Change (%)	p Value
1A	67 ± 5	74 ± 7	11.1 ± 5.1	<0.01
1B	66 ± 2	73 ± 4	11.5 ± 5.8	<0.01
1C	65 ± 6	66 ± 4	1.6 ± 9.1	NS
			8.4 ± 7.0	
2A	67 ± 3	73 ± 5		<0.01
2B	67 ± 4	70 ± 5	4.3 ± 4.4	NS
2C	61 ± 10	64 ± 9	5.4 ± 6.7	NS

Values are mean ± SD.
NS = not significant.

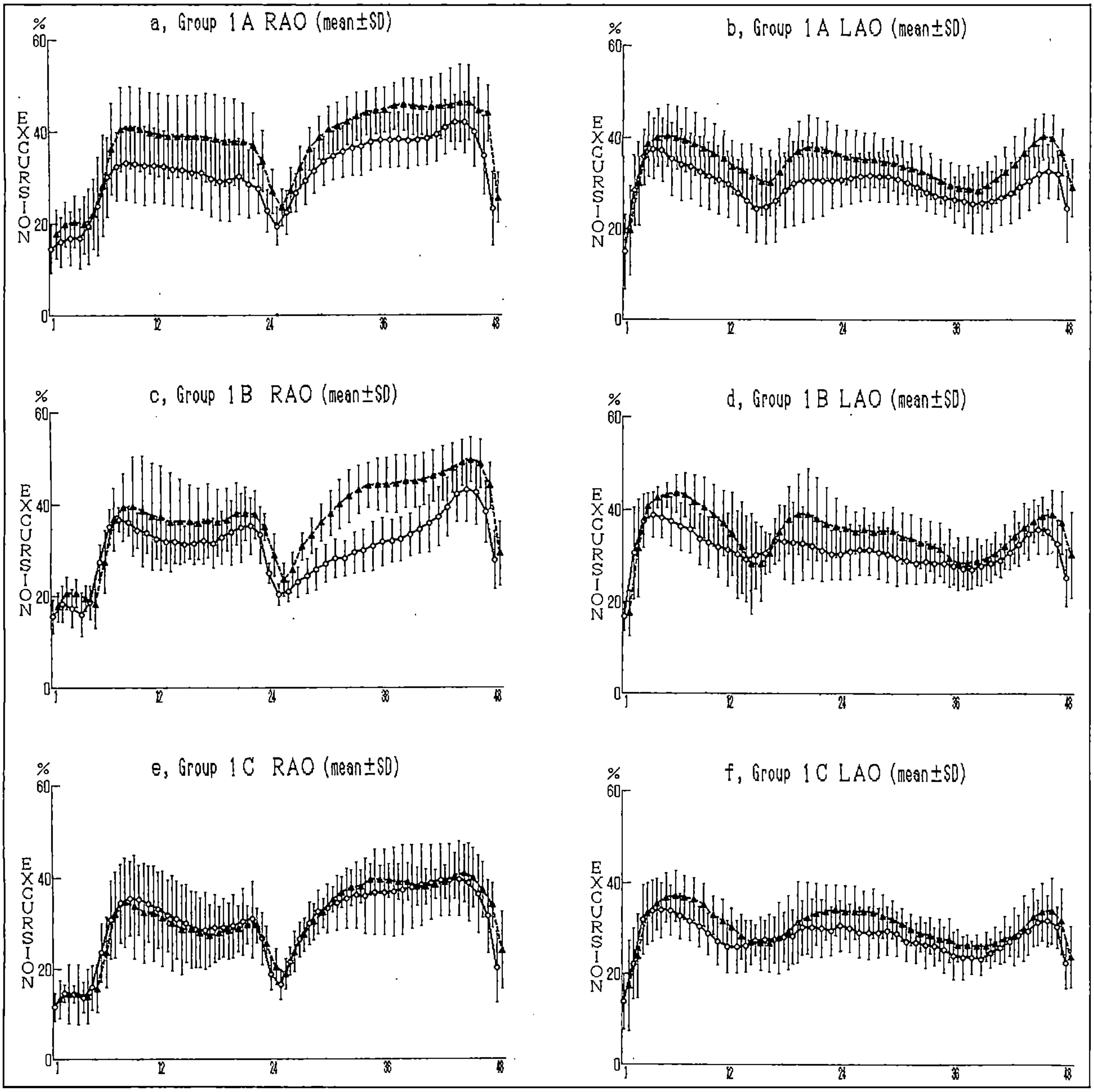

FIGURE 2. Changes in left ventricular wall motion in the acute phase groups. *Open circles* show wall motion before dipyridamole infusion; *closed circles* show wall motion after dipyridamole infusion. Group 1A *(a, b)*: Radial shortening in every left ventricular segment increased significantly after dipyridamole infusion. Group 1B *(c, d)*: Radial shortening in the apical, anterolateral, anterobasal and posterolateral segments increased significantly after dipyridamole infusion. Group 1C *(e, f)*: There were no significant changes in radial shortening after dipyridamole infusion in the segments. LAO = left anterior oblique view; RAO = right anterior oblique view.

(excursion) was calculated. The left ventricle was subdivided into 5 segments in the right anterior oblique view, and 3 segments in the left anterior oblique view. Radius numbers 1 to 8 were posterobasal, 9 to 20 were inferior, 21 to 28 were apex, 29 to 40 were anterolateral and 41 to 48 were anterobasal in the right anterior oblique view. Radius numbers 1 to 16 were septal, 17 to 25 were apex and 26 to 48 were posterolateral in the left anterior oblique view.

LV end-diastolic and end-systolic volumes were calculated by the area-length method,[10] and global ejection fraction was calculated.

Statistical analysis: All data were expressed as mean ± SD. The statistical analysis for differences in mean value was performed using the Wilcoxon Mann-Whitney test. A p value <0.05 was considered significant.

RESULTS

Hemodynamic effect of dipyridamole (Tables I and II): Heart rate increased significantly in every group. Systolic and diastolic blood pressure decreased significantly in every group.

Changes in global ejection fraction due to dipyridamole (Table III): Global ejection fraction in groups 1A, 1B and 2A increased significantly after dipyridamole infusion, but there were no significant changes in ejection fraction in groups 1C, 2B and 2C.

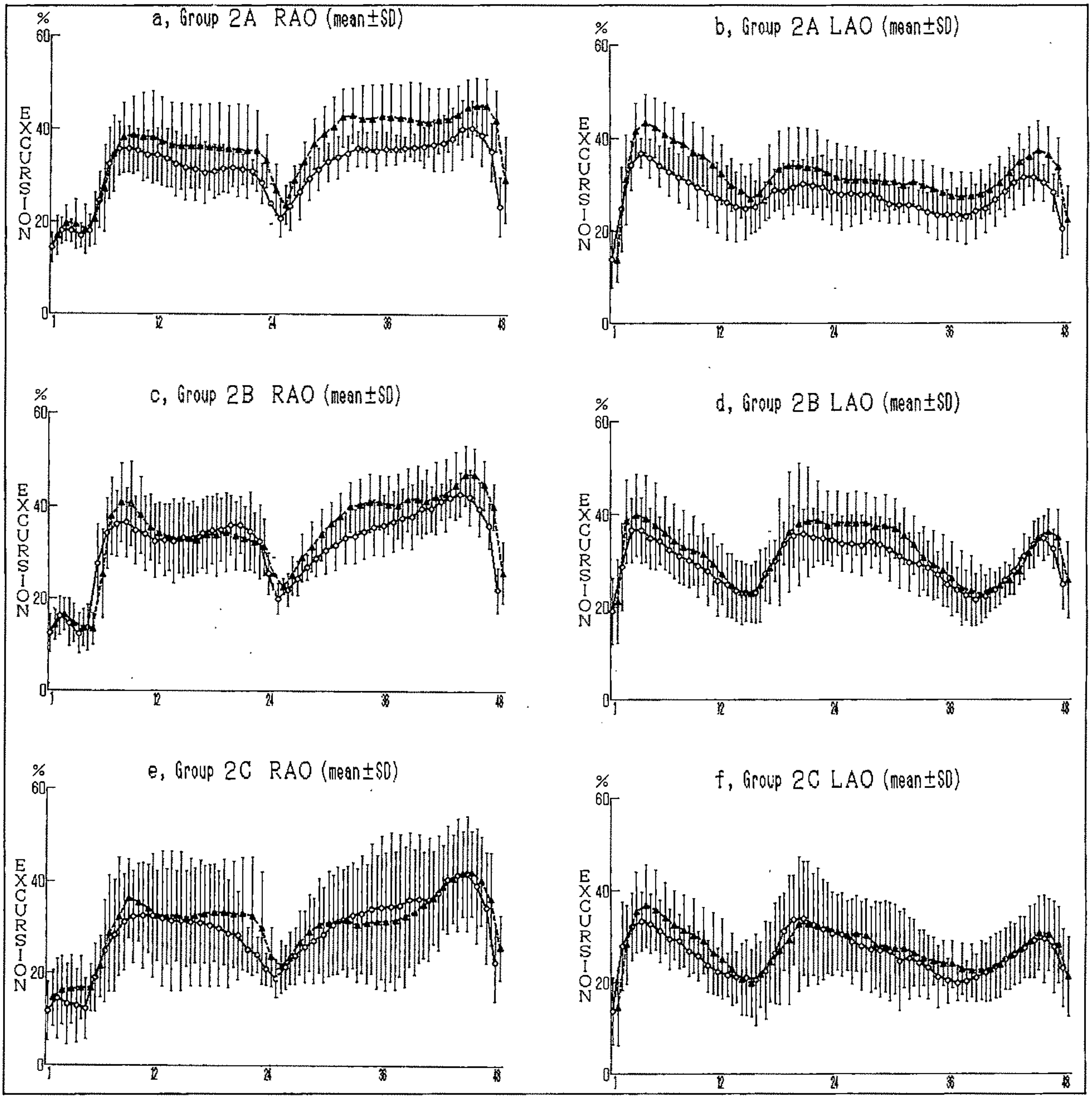

FIGURE 3. Changes in left ventricular wall motion in the chronic phase groups. *Open circles* show wall motion before dipyridamole infusion; *closed circles* show wall motion after dipyridamole infusion. Group 2A *(a, b)*: Radial shortening in apex, anterolateral, septal and posterolateral segments increased significantly after dipyridamole infusion. Group 2B *(c, d)* and 2C *(e, f)*: There were no significant changes in radial shortening after dipyridamole infusion in the segments. Abbreviations as in Figures 1 and 2.

Changes in left ventricular wall motion due to dipyridamole (Figures 2 and 3): ACUTE PHASE GROUPS (GROUP 1A, 1B, 1C): Figures 2 and 3 show wall motion before and after dipyridamole infusion. The percent radial shortening was described in radius numbers 1 through 48. Numbers 1, 12, 24, 36 and 48 denote radius of the left ventricle. Statistical analysis was performed for differences in the mean values of subdivided segmental radial shortening before and after dipyridamole infusion in each of the subdivided 8 segments (right anterior oblique, 5 segments; left anterior oblique, 3 segments) of the left ventricle.

In group 1A, the radial shortening in every LV segment increased significantly after dipyridamole infusion (Figure 2, a and b). In group 1B, the radial shortening in the apical, anterolateral, anterobasal and posterolateral segments increased significantly after dipyridamole infusion (Figure 2, c and d). In group 1C, there were no significant changes in radial shortening after dipyridamole infusion in the segments (Figure 2, e and f).

CHRONIC PHASE GROUPS (GROUP 2A, 2B, 2C): In group 2A, radial shortening in the apex, anterolateral, septal and posterolateral segments increased significantly after dipyridamole infusion (Figure 3, a and b). In group 2B and 2C, there were no significant changes in radial shortening after dipyridamole infusion in the segments (Figure 3, c to f).

Patients with hypokinetic segments of left ventricular wall motion (Figure 4): Regional LV wall motion abnormalities were evaluated in the following manner: the mean − 2 SD was adjusted for radial shortening of each LV segment in group 1A as a control. In every segment of each group, when the mean segmental radial shortening was less than the control value (mean − 2 SD of corresponding segment in group 1A), it was identified as hypokinesia. Patients who had ≥1 LV hypokinetic segment were termed "hypokinetic patients."

In group 1A, 8% (2 of 24) were hypokinetic patients before and after dipyridamole infusion. In group 1B, 22% (2 of 9) were hypokinetic patients before dipyridamole infusion, and there were no hypokinetic patients after dipyridamole infusion. In group 1C, 8% (1 of 12) were hypokinetic patients before dipyridamole infusion, but hypokinetic patients increased to 42% (5 of 12) after dipyridamole infusion.

In group 2A, the pattern of regional LV wall motion with dipyridamole was similar to that in group 1A, but 23% (3 of 13) were hypokinetic patients before and 38% (5 of 13) were hypokinetic patients after dipyridamole infusion. In group 2B, 13% (1 of 8) were hypokinetic patients before and 38% (3 of 8) were hypokinetic patients after dipyridamole infusion. In group 2C, 40% (4 of 10) were hypokinetic patients before dipyridamole infusion, and hypokinetic patients increased to 70% (7 of 10) after dipyridamole infusion.

DISCUSSION

Recently, several methods have been used to evaluate LV function in patients with Kawasaki disease (e.g., LV cineangiography,[8] 2-dimensional echocardiography[9] and thallium-201 scintigraphy).[11] Analysis of LV wall motion by cineventriculography is one of the methods to evaluate LV function in an attempt to quantify endocardial movement.

When the analysis of LV wall motion is performed, a superimposition of an end-diastolic and end-systolic LV silhouette is necessary.[12] The floating internal reference system was used, because the cardiac silhouette itself may move during filming in children because of their breathing.

There are several methods to quantify LV wall motion (e.g., the radial method, chord method and center line method).[13] All these methods follow the hypothesis that LV endocardium moves to the center point or center line which is set up artificially. In this study, the radial method was used to evaluate LV wall motion. The apical point and the long axis were determined in this method, and the aortic valve portion that was not related to contraction was excluded.

On the other hand, the effect of dipyridamole is linked to the metabolism and transport of adenosine, which is a conductor of coronary blood flow and coronary vasodilation.[14] Dipyridamole appears to act predominantly on the small resistance vessels of the coronary artery bed and it alters transcapillary exchange in the same way as does severe hypoxia.[15] Thus, it appears to have little effect on vascular resistance areas where small vessels are already maximally dilated by proximal coronary artery stenosis. The regional ischemia occurring after dipyridamole infusion in a region supplied by

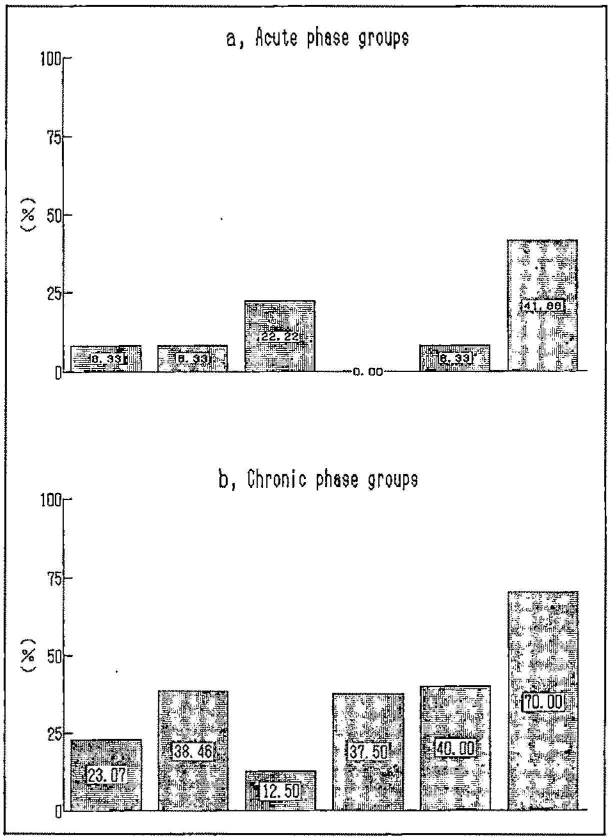

FIGURE 4. Patients with regional left ventricular hypokinesia. Percentage of patients who had at least 1 left ventricular hypokinetic segment. (Hypokinetic segment: mean segmental radial shortening <mean − 2 SD of corresponding segment in group 1A.)

the stenotic coronary artery is accounted for by local imbalance between myocardial oxygen supply and demand resulting from vertical steal or horizontal steal, or both.[16]

Dipyridamole is also related to systemic blood pressure and the peripheral blood flow. After dipyridamole administration, peripheral vasodilation evokes an increase in heart rate and decrease in blood pressure; as a result, an increase in cardiac output is observed.[17] In this study, heart rate increased and blood pressure decreased significantly in every group. These changes would be expected to result from dipyridamole's effect of peripheral vasodilation.

There are several causes for LV dysfunction in Kawasaki disease. First, there is myocardial involvement resulting from myocarditis in the acute phase of illness. In this study, 8% of group 1A patients (with normal findings on the coronary angiogram) had abnormal LV wall motion. Second, there is myocardial involvement resulting from coronary artery stenosis with myocardial ischemia. Coronary aneurysms often lead to coronary stenosis and obstruction when the maximal diameter is >8 mm.[18] Myocardial infarction and abnormal LV wall motion occur in such patients. However, it is known that the coronary lesion has subsequent regression when the maximal diameter is <8 mm.[18] Our study raised some interesting points concerning the relation between coronary lesions and LV function in patients with Kawasaki disease.

Analysis of left ventricular function during the acute phase: The pattern of LV wall motion with dipyridamole in group 1B was similar to that on group 1A. However, in group 1C there was no significant change in ejection fraction or in LV wall motion pattern with dipyridamole. These results appear to be related to the coronary vasodilation associated with dipyridamole, because there was no significant change in heart rate or blood pressure responses to dipyridamole between the acute phase groups. In some patients in group 1C, the distensibilities of the affected coronary arteries with dipyridamole were lower than those of normal coronary regions, and the reduction in coronary blood flow to the distal myocardial regions of the affected coronary arteries was considered to occur. In such patients, abnormal LV wall motion was detected.

There are dilated lesions and stenotic lesions in Kawasaki disease. Previous researchers reported that abnormal LV wall motion tended to be detected in patients with stenotic coronary lesions.[8] In this study, there were several patients with abnormal LV wall motion in the group with dilated coronary lesions only, and the abnormality was considered to be detected by dipyridamole infusion.

Analysis of left ventricular wall motion during the chronic phase: The pattern of LV wall motion in group 2A was similar to that in group 1A, but in 38% of group 2A patients, abnormal LV wall motion after dipyridamole infusion was detected. This means that there were some patients whose dilated coronary arteries improved to normal with dilatation, but the responsiveness to dipyridamole did not. Thus, in such patients abnormal LV wall motion occurred after dipyridamole infusion resulting from the local imbalance of blood flow.

In group 2C, 40% were hypokinetic patients before and 70% after dipyridamole infusion. Thus, in such patients with coronary stenosis, regional ischemia in a region supplied by a stenotic coronary artery tended to occur and regional asynergy was caused by dipyridamole infusion.

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Effect of Fat-Modified and Fruit- and Vegetable-Enriched Diets on Blood Lipids in the Indian Diet Heart Study

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This study was designed to test the efficacy of the administration of fruits and vegetables for 12 weeks as an adjunct to a prudent diet in decreasing blood lipids in 310 (intervention; group A) and 311 (control; group B) patients with risk factors of coronary artery disease (CAD) in a parallel, single-blind fashion. At entry to the study, sex, mean age, body weight, body mass index, systolic and diastolic blood pressures, and blood lipoproteins were comparable between both groups. Tasty fruits and vegetables were given to patients to eat before major meals for better nutrient adherence and adequacy. Dietary intakes were determined by questionnaires and by weighing of fruit and vegetable intake. Fruits and vegetables decreased total cholesterol level by 6.5% and low-density lipoprotein cholesterol level by 7.3% in group A, whereas the levels were unchanged in group B. The high-density lipoprotein cholesterol levels that decreased during the diet stabilization period in both groups, increased by 5.6% in group A after 12 weeks. Serum triglycerides also decreased (7%) more in group A than B. Fasting blood glucose decreased by 6.9% in group A and by 2.6% in group B. The combined effect of a fat-modified diet plus fruits and vegetables was greater than these changes. Because tasty fruits were taken by the patients before meals (when they are hungry) and are easily available at reasonable cost in our marketing and buying capacity, the compliance was excellent. It is possible that fruits and vegetables may be a safe adjunct to a prudent diet in free-living subjects with risk factors of CAD for the modulation of blood lipoproteins and for the prevention of CAD.

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In most developing countries, there has been a rapid increase in coronary artery disease (CAD).[1] In South Asian immigrants in the United Kingdom,[2] a rapid death rate for CAD has been related to modest changes in risk factors[3] such as glucose intolerance, insulin resistance, low high-density lipoprotein (HDL) cholesterol and hypertriglyceridemia. Because most of these risk factors are related to diet,[4–6] there is an ongoing effort to increase public awareness regarding a prudent diet[5] and develop new, safe methods to decrease serum cholesterol levels in patients in whom adjunctive therapy may be desirable. Whereas drugs work by different mechanisms, each drug also has its own side effects. Several studies have demonstrated a reduction in cardiovascular events in patients independently treated with lipid-lowering drugs and a fat-modified diet. No study to date has shown a favorable effect on the overall death rate.[7,8] It appears that there is a need to modify our approach for decreasing serum cholesterol, which should be safe and also counteract other multiple mechanisms[3,9] underlying CAD. One such suggested new approach showed that foods containing water-soluble fibers[10–13] such as oat bran, certain legumes, and fruits and vegetables can effectively decrease serum cholesterol without significant risk. Apart from the modulation of blood lipoproteins, a fruit- and vegetable-enriched diet may also inhibit hyperinsulinemia,[4,14] hyperglycemia, hypertriglyceridemia and hypertension, and provide antioxidant[4,9] vitamins and minerals that are known to be protective against CAD.

In a current approach,[11] 10.2 g/day of psyllium hydrophilic mucilloid was administered for 8 weeks after initiation of the American Heart Association Step I diet.[5] There were 4.8 and 8.2% reductions in total and low-density lipoprotein (LDL) cholesterol levels, respectively. Similar observations[12,15,16] were made in other trials using soluble fiber by this approach. In the present study, we examined the effect of fruits and vegetables, in a randomized and controlled manner (possibly for the first time in a large number of patients by the current approach), on blood lipoprotein levels in patients with risk factors of CAD. Patients received a 4-week initial diet therapy with a fat-modified, prudent diet, followed by 12 weeks of treatment with fruits and vegetables in the intervention group.

METHODS

Patients were recruited through advertisements in local clubs, clinics and newspapers from the middle socioeconomic class during a period of 2 years and had a

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proven diagnosis of either angina pectoris, myocardial infarction or major risk factors of CAD. Of 1,050 respondents, 653 subjects volunteered to participate in the trial. During the observation period, all patients were asked to maintain their usual lifestyle and dietary habits, and daily drug and dietary diaries. Clinical, electrocardiographic, radiologic and laboratory data were obtained in all subjects before admission to the study. Exclusion criteria were chronic diseases such as diarrhea, dysentry, blood urea of 40 mg/dl (6.6 mmol/liter) and cancer. Blood pressures (systolic and diastolic phase V of Korotkoff) were measured after 5 minutes of rest lying comfortably in the supine position by a single-mercury sphygmomanometer and by the same clinician. Electrocardiograms after exercise (bicycle ergometer [$n = 591$] and treadmill test [$n = 36$]) were obtained in all patients to find the extent of CAD. Nutrient intakes before entry to the study were obtained by 24-hour dietary recalls.

Essential hypertension was diagnosed as blood pressure $>150/95$ mm Hg, diabetes mellitus by a positive glucose tolerance test showing fasting blood glucose at >110 mg/dl (6.1 mm/liter) and postprandial 2 hours after 75 g of oral glucose at >140 mg/dl (7.7 mmol/liter), hypercholesterolemia by serum cholesterol >250 mg/dl (6.47 mmol/liter), hypertriglyceridemia by serum triglyceride >190 mg/dl (2.14 mmol/liter), and smoking by consumption of ≥ 1 cigarette/day. Overweight was considered a body mass index >25 kg/m^2 and obesity an index >30 kg/m^2, alcohol abuse by consumption of >60 g/week of alcohol, and physical inactivity by <1 km/day of walking during daily activities. All patients with the diagnoses of angina pectoris (mean 7.6 months) or myocardial infarction (mean 56.5 days) were receiving treatment for 1 month to 1 year, with a proven diagnosis based on criteria set forth by the World Health Organization.[17]

Study design: The study comprised a 3-week observation period and 4-week diet stabilization period, followed by a 12-week treatment period. After giving written informed consent, all patients were closely observed for 3 weeks, during which they were asked to maintain their usual lifestyle, daily drug intake and dietary diaries. After dietary records were reviewed for pretrial nutrient intakes, a dietitian, physician and pharmacists stratified patients as to different risk factors such as serum cholesterol level >240 mg/dl, age >50 years, body mass index >25 kg/m^2, and presence of angina pectoris or myocardial infarction. After stratifications, patients with each risk factor in each group were assigned to diet A or B by blindly selecting a card from a stack with equal numbers of each. Thus, patients with each risk factor and those with CAD were divided into 2 approximately equal groups to receive either diet A or B, while the responsible physician was unaware of the assigned dietary regimen. At the beginning of the diet stabilization period, all patients were instructed to follow the American Heart Association Step I diet[5] (total calories from fat <30%, polyunsaturated/saturated fat ratio 1, and <300 mg/day of dietary cholesterol) for 4 weeks. Dietary intakes were obtained through questionnaires by 24-hour dietary recall in both groups; group A patients were advised to consume ≥ 400 g/day of fruits and vegetables, and plenty of legumes and cereals. Group A comprised 310 patients on diet A (rich in fruits, vegetables and legumes) in conjunction with a prudent diet, and group B comprised 311 receiving only a prudent diet according to the advice provided by the dietitian. Hypolipidemic drugs were not administered to any patient. In both diets A and B, meat, eggs, hydrogenated solid oils, butter and clarified butter were replaced with cottage cheese, oils of soybean, ground nuts and sunflower, with the aim of providing prudent diets and keeping the diets isocaloric. Diet A also included plenty of fruits such as guava, grapes, papaya, bananas, sweet limes, oranges and apples, vegetables such as leaves of fenugreek, spinach, mustard, radishes, tomatoes, lotus root, bitter gourds, mushrooms, onions, garlic and trichosanthes, condiments such as black paper and fenugreek seeds, cereals such as grams, peas, kidney and red beans, and nuts such as almonds and walnuts.

The intervention diet was administered in a food to eat approach, with an emphasis on eating the aforementioned foods without much emphasis on restriction of foods rich in saturated fat and cholesterol (to encourage patient cooperation), and patients were advised to eat tasty fruits and vegetables such as guava, tomatoes, papaya, apples, carrots and cucumbers before major meals when they were hungry, to avoid foods rich in energy, saturated fat and cholesterol, and achieve better nutrient adherence and adequacy. The aim was to provide plenty of soluble dietary fiber, and antioxidant vitamins and minerals.

Data collection: Nutrient intakes were obtained by computation of the Indian food composition table based on the results of dietary adherence determined by differences in the weight of fruit and vegetable intake, and dietary questionnaires in both groups. Body weights were measured at each visit by the pharmacist independently at weeks 2, 4, 6 and 16 (after removing clothes and shoes) to the nearest 0.1 kg. Every effort was made to obtain data on diet and drug intake, exercise, adverse events, smoking, weight reduction and hospitalization in both groups. Smoking habits were recorded in terms of the daily consumption of tobacco. Occupational and leisure time, and physical activities were assessed with the Indian classification of activities based on occupation,[18] with the use of a 4-point scale adapted from the Gothenburg study.[19] Dietary intakes were obtained before entry to the study, after 4 weeks of the diet stabilization period and after another 12 weeks of dietary advice by 24-hour dietary recall based on the weighing of fruit and vegetable intake and on a questionnaire completed to assess the effect of dietary advice.

Information from the questionnaires regarding dietary adherence was quantified by a formula. A total score of 1 indicated 100% adherence to the recommended changes in diet and 0 indicated no adherence. Patients who adhered more than our minimal recommendations (400 g/day of fruits and vegetables) achieved a score >1, and those who consumed <400 g/day of fruits and vegetables were given a score <1. These

TABLE I Baseline Means and SD of Demographic Profile of Subjects in the Indian Diet Heart Study

	Intervention Group (n = 310)			Control Group (n = 311)		
	Baseline	After Diet	After Therapy	Baseline	After Diet	After Therapy
Men/women	262/48	262/47	260/46	269/42	218/41	267/41
Mean age (year)	46.3 (8.6)	—	—	47.8 (8)	—	—
Body weight (kg)	64.8 (7.3)	64.4 (6.8)	63.1 (5.8)	65.9 (7)	65.4 (6.8)	64.8 (6.3)
Body mass index (kg/m^2)	24.3 (3.4)	24.2 (3)	24.0 (2.8)	24.8 (5.1)	24.6 (5)	24.4 (4.4)
Blood pressure (mm Hg)						
Systolic	133.6 (18.3)	130.0 (14.4)	124.1 (11.5)*	132.3 (15.6)	127.3 (13.2)	127.8 (12.1)
Diastolic	86.3 (10.2)	82.3 (6.5)	78.2 (5.1)*	86.8 (9)	88.5 (7.5)	84.5 (8.2)

*p value significant by comparing changes (from baseline to posttherapy levels) in groups A and B by 2 sample *t* tests using 1-way analysis of variance ($p < 0.05$).

TABLE II Nutrient Intake During Different Periods of Follow-Up

	Intervention Group (n = 310)			Control Group (n = 311)		
Variable	Baseline	After Diet	After Therapy	Baseline	After Diet	After Therapy
Total energy (KJ/day)	9,037.4 (686)	7,884 (667)	7,810.0 (643.5)*	9,129.5 (702.9)	8,984.0 (692.5)	7,931.5 (684)
Dietary components (% of total energy/day)						
Total protein	15.8 (0.54)	15.6 (0.54)	14.5 (0.54)	15.1 (0.53)	15.2 (0.53)	15.0 (0.53)
Total carbohydrates	57.4 (1.61)	58.0 (1.62)	61.0 (1.63)†	56.4 (1.6)	56.6 (1.6)	57.5 (1.6)
Total fatty acids	26.8 (0.84)	26.4 (0.34)	24.5 (0.84)†	28.5 (0.86)	28.2 (0.86)	27.5 (0.86)
Saturated	12.2 (0.68)	8.7 (0.56)	8.0 (0.56)*	12.2 (0.68)	10.5 (0.67)	10.0 (0.67)
Monounsaturated	7.0 (0.54)	8.9 (0.56)	8.0 (0.56)	9.2 (0.58)	8.7 (0.58)	9.4 (0.58)
Polyunsaturated	7.6 (0.55)	8.8 (0.56)	8.5 (0.56)	7.1 (0.54)	9.0 (0.54)	9.1 (0.55)
Polyunsaturated/saturated fat ratio	0.62 (0.03)	1.01 (0.04)*	1.06 (0.04)†	0.58 (0.03)	0.85 (0.04)*	0.81 (0.04)
Cholesterol (mg)	302.5 (30.5)	225.5 (22.2)*	195.0 (18.4)†	316.5 (32.4)	265.5 (26.4)*	290.5 (28.6)
Alcohol (g/week)	51.6 (38.8)	41.2 (26.5)	40.2 (24.6)*	48.6 (40.5)	43.4 (30.4)*	42.0 (28.5)
Total fiber (g/day)	24.2 (7.8)	25.4 (7.6)	48.4 (12.3)†	26.6 (8.8)	24.3 (8.4)	28.6 (9.5)
Water soluble	11.2 (4)	12.2 (4.1)	33.2 (7.6)†	12.2 (4.5)	12.0 (4.5)	15.4 (5.6)
Water insoluble	13.0 (3.1)	13.2 (3.2)	15.2 (4.4)	14.4 (5.1)	12.3 (4.6)	13.2 (4.6)
Salt (g/day)	8.6 (0.78)	8.4 (0.78)	8.1 (0.77)	8.8 (0.78)	9.1 (0.78)	9.2 (0.78)
Ascorbic acid (mg/day)	86.5 (13.6)	92.4 (14.5)	410.0 (75.5)†	96.5 (15.4)	94.3 (14.1)	198.4 (22.6)*
Potassium (mg/day)	1,112.6 (196)	1,150.0 (205)	2,512.0 (176)†	1,108.4 (19.5)	1,121.0 (195.4)	1,275.0 (205)
Magnesium (mg/day)	370.5 (85.5)	375.4 (88.7)	985.2 (185)†	380.0 (185)	385.0 (170)	410.0 (185)
Copper (mg/dl)	2.0 (0.4)	2.1 (0.4)	5.1 (0.75)†	2.1 (0.4)	2.0 (0.4)	2.2 (0.41)
Total fruits and vegetables (g/day)	256.4 (45.8)	262.5 (48.7)	592.0 (112.5)†	261.4 (47.8)	265.8 (52.5)	278.5 (65.5)
Total adherence score (%)	54.0 (31)	96.0 (42)	111.0 (60)†	53.0 (31)	93.0 (40)*	71.0 (40)

*p value significant by intragroup comparison of baseline to postdiet ($p < 0.05$) and posttherapy ($p < 0.01$) levels in both groups using Student's *t* test.
†p value significant ($p < 0.01$) by comparison between posttherapy levels of intervention and control groups using Student's *t* test.

scores were multiplied by 100 to convert them into percentages.

Laboratory data: Laboratory data were obtained at entry, and after 4 and 12 weeks in all subjects. A venous blood sample was obtained in a fasting state and analyzed for urea, glucose, triglycerides,[20] cholesterol,[21] blood counts and hemoglobin in all subjects. Total cholesterol was measured directly in the serum, and HDL cholesterol was measured after precipitation of very low density lipoprotein and LDL cholesterol, and LDL cholesterol was measured by an enzymatic method.[21] Because of the high expense, LDL and HDL cholesterol were not obtained in some low-income patients.

Statistical methods: Student's *t* test and 2 sample *t* tests using 1-way analysis of variance were used for the analysis of data. A value <0.05 and 2-tailed was considered statistically significant for comparison of 2 groups of data. All data were analyzed for 4 and 12 weeks on the basis of intention to treat. The last values of clinical and laboratory data recorded in patients who did not complete the study were incorporated in all outcome analyses of data at 4 and 12 weeks.

RESULTS

After a 3-week observation period of 653 respondents, those with diarrhea, dysentery uremia or cancer (n = 26) and those who did not like the intervention diet (n = 6) were excluded. Groups A and B had comparable prerandomization characteristics with respect to age, sex, weight, body mass index, blood pressures (Table I) and laboratory data, indicating effective randomization (Tables I to III). The numbers of patients with risk factors such as hypertension (99 vs 100 cases), hypercholesterolemia (45 vs 43), diabetes mellitus (54 vs 50), hypertriglyceridemia (22 vs 20), obesity (99 vs 100), physical inactivity (162 vs 159), alcohol abuse (54 vs 57), family history (22 vs 20) and CAD (118 vs 122) were comparable between groups A and B. Smoking was slightly more frequent in group A than B (106 vs 101 cases). Drug therapy, including propranolol (40 to

TABLE III Changes in Laboratory Data from Baseline in Intervention and Control Groups

	Intervention Group (n = 310)			Control Group (n = 311)			Net Change (%)†
Variable*	Baseline	After Diet	After Therapy	Baseline	After Diet	After Therapy	
	mean (standard Deviation) m mol/L						
Total cholesterol	6.31 (1.14)	6.12 (1.1)	5.71 (0.85)‡§	6.37 (1.2)	6.23 (1.16)	6.23 (1.14)	
Change from baseline (%)	—	−3.1	−9.6		−2.2	−2.3	6.3†
Change from after diet (%)	—	—	−6.5	—	—	−0.1	
LDL cholesterol	4.35 (2.2)	4.20 (2.02)	3.88 (1.86)*‡§	4.29 (2.12)	4.18 (2.1)	4.17 (2.02)	
Change from baseline (%)	—	−3.5	−10.8	—	−2.5	−2.8	8.0†
Change from after diet (%)		7.3	−7.3			−0.3	
HDL cholesterol	1.20 (0.21)	1.19 (0.21)	1.25 (0.22)§	1.17 (0.22)	1.15 (0.21)	1.14 (0.21)	
Change from baseline (%)		−1.1	+4.5		−1.6	−2.8	7.3†
Change from after diet (%)			+5.6			−1.2	
Triglycerides	1.70 (0.21)	1.70 (0.2)‡	1.57 (0.16)‡§	1.81 (0.23)	1.77 (0.22)	1.73 (0.2)	
Change from baseline (%)		−5.2	−12.2		−2.3	−4.5	7.7†
Change from after diet (%)			−7.0			−2.2	
Fasting blood glucose	5.97 (1.43)	5.63 (1.32)‡	5.22 (1.11)‡§	6.04 (1.57)	5.38 (1.52)	5.72 (1.48)‡	
Change from baseline (%)		−5.7	−12.6		−2.7	−5.3	7.3
Change from after diet (%)			−6.9			−2.6	

*Net change (final change in group A − final change in group B) significant ($p < 0.01$).

†At baseline, laboratory data were available for all patients and at end of study for 305 group A and 304 group B patients, except for HDL and LDL cholesterol, which were available only for 186 both at baseline and at end of study.

‡Significant change from baseline ($p < 0.05$); §significant change from postdiet ($p < 0.05$).

p value significant by comparison of changes from baseline to postdiet and posttherapy levels within groups, and changes after therapy between groups A and B by 2 sample *t* tests using 1-way analysis of variance.

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

240 mg/day; 50 vs 47 cases), thiazide, (25 to 60 mg/day; 60 vs 49 cases), furosemide (20 to 80 mg/day; 45 vs 42 cases) and nifedipine (20 to 60 mg/day; 130 vs 116 cases), was similar in both groups, except for slightly more propranolol in group B and more thiazide in group A. Changes in mean body weight (1.7 vs 1.1 kg) after the therapy period were similar in both groups (Table I).

There were 4 withdrawals from group A and 3 from group B during 16-week follow-up; these patients were either lost to follow-up or did not follow the intervention diet. Apart from these cases, 50 patients in group A and 42 in group B missed follow-up visit for 1 to 4 weeks; however, they were following the advised diets and rejoined their respective groups. Withdrawals from group A had a decrease in blood lipids, indicating that these subjects were following the dietary advice.

At baseline, nutrient intakes were similar in both groups. After 4 weeks on the fat-modified diet, both groups had significantly lower intakes of dietary cholesterol and saturated fat, and higher polyunsaturated/saturated fat ratios than at baseline (Table II). After a further 12 weeks, dietary questionnaires showed that group A had a significantly higher amount of total and water-soluble dietary fiber, ascorbic acid, potassium, magnesium and copper than did group B, and also compared with that at 4 weeks. Group A consumed a significantly higher amount of fruits and vegetables than did group B. The total adherence score was also significantly higher in group A than B (Table II). Whereas both groups received a fat-modified diet at 4 weeks, only group A received soluble dietary fiber, vitamins and minerals after 4 weeks. Compliance was good because fruits and vegetables are tasty and easily available at reasonable prices. There were no side effects observed, except for some belching, fullness and loose stools at the beginning in some patients.

Small reductions in total (3.1 vs 2.2%), LDL (3.5 vs 2.5%) and HDL (1.1 vs 1.6%) cholesterol levels in groups A and B, and significant decreases in triglycerides (5.2 vs 2.3%) and fasting blood glucose (5.7 vs 2.7%) in group A compared with baseline levels were observed after 4 weeks of the diet stabilization period. In group B, the changes were insignificant.

After 12 weeks in the treatment period, there were significant reductions in total and LDL cholesterol, triglycerides, fasting blood glucose and blood pressures in group A compared with at baseline and to post-diet levels and changes in group B. Whereas HDL cholesterol showed a decrease at 4 weeks, it increased after 12 weeks compared with at baseline and to post-diet levels and changes in group B. In group B, the changes in lipids were insignificant, except for a reduction in fasting blood glucose at 12 weeks compared with at baseline (Table III).

DISCUSSION

There is evidence[4,9,22] that increased intake of soluble fiber and antioxidants may be protective against chronic diseases, including CAD. This evidence has led to the recommendation by the World Health Organization Expert Committee[23] to consume ≥400 g/day of fruits and vegetables for prevention. Revised dietary guidelines[24] for Americans recommend "a diet with plenty of vegetables, fruits and grain products." The National Cholesterol Education Program Adult Treatment Panel[5] has also acknowledged the cholesterol-lowering ability of water-soluble dietary fiber, and the American Medical Associations Council on Scientific Affairs[13] advised that fiber-rich foods are important for a healthy diet. In view of these recommendations, the results of this study may be of great significance.

The Indian Diet Heart Study is the first randomized and controlled intervention trial showing that the new approach of using a fat-modified diet plus soluble dietary fiber can be successfully applied to a large number of patients with risk factors of CAD outside the hospital (for ≥16 weeks). The intervention diet, consisting of oils plus fruits, vegetables and cereals, appears safe and compatible with other treatment of risk factors of CAD. The changes in serum lipid levels, consisting of a 6.5% reduction in total cholesterol and a 7.3% decrease in LDL cholesterol with a 315 g/day net increase in the intake of fruits and vegetables, are comparable with similar reductions in lipid levels observed in other studies using this approach in <100 patients with or without hyperlipidemia.[10–12] Contrary to our study, those and other studies[10–12,15,16] used oats or psyllium (after initiation of a fat-modified diet) that lack antioxidant vitamins and minerals.

The consumption of dietary soluble fiber may be increased by eating a variety of fruits and vegetable, legumes, oats, psyllium, pectin and guar gum.[13] However the exact mechanism of their action and how they influence blood lipids are not known. Sequestration of bile salts may interfere with micellar solubilization and diffusibility of cholesterol and fatty acids, which may lead to increased fecal bile acid content and a reduction of the cholesterol pool. There may be an increased binding of soluble fiber with products of fat digestion, fatty acids and monoglycerides. Certain plant fibers, such as pectin, may enhance the formation of short-chain fatty acids that may inhibit cholesterol synthesis.[13]

In 1 recent trial,[16] a combination of fat-modified and oatbran-enriched diets decreased serum cholesterol by 10 to 17% in free-living patients with hypercholesterolemia. It appears that the combined effect of this approach, especially in hyperlipidemic patients, may be as successful in lowering lipid levels as is drug therapy, but with fewer side effects and less expense.[25] In the Indian Diet Heart Study, the combination of fruits and vegetables (522 g/day) and a fat-modified diet decreased serum total cholesterol by 9.6%, LDL cholesterol by 10.8% and triglycerides by 12.2% compared with initial levels, with insignificant changes in group B. Part of the decrease in triglycerides in the 2 groups may be due to mild decreases in mean body weight (1.7 and 1.1 kg, respectively). Because both groups A (9.5/8.1 mm Hg) and B (5.5/2.3 mm Hg) showed a decrease in mean blood pressures at the end of the trial, it appears that the intervention had no adverse effect on absorption[13] of nutrients and antihypertensive drugs. The decrease in blood pressures in group A was significant. Fasting blood glucose levels were decreased in both groups (more in group A than B) (Table III).

Apart from the decrease in serum total and LDL cholesterol and triglycerides, the present study also showed a significant net increase in HDL cholesterol in group A compared with initial levels (5.6%) and to changes in group B (7.3%). After 4 weeks on a fat-modified diet, both groups A and B showed a minor decrease in HDL cholesterol. The increase in HDL after 12 weeks of intake of fruits and vegetables may be due to dietary minerals and vitamins[4] or reflect compensating homeostatic changes that returned HDL cholesterol to normal levels.

In large dietary trials, compliance with dietary advice is a problem, because patients may not exactly eat what they are advised and the control group also may share the intervention program. Assessment of dietary intake by questionnaires (although fruit and vegetable intake was weighed in this study) is also open to bias, because subjects may have learned simply how to answer what the dietitian wants to hear. However, the presence of a risk factor or CAD in the Indian Diet Heart Study and the weighing of fruit and vegetable intake may have motivated patients to eat what they were advised. Furthermore, patients were advised to eat tasty fruits before meals, which may have improved compliance. It appears that in patients with risk factors, a fat-modified diet plus fruits and vegetables are safe methods to decrease blood lipids and possibly other risk factors of CAD. Fruits and vegetables may be preferred over oats and psyllium, because they also caused a decrease in serum triglycerides and fasting blood glucose, and an increase in HDL cholesterol, and provide antioxidants that are protective against CAD. Long-term follow-up may be necessary to confirm the efficacy of this approach on coronary events. The addition of exercise and weight reduction in the intervention program is likely to enhance the efficacy of this approach in the prevention of CAD.

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Incidence, Pathophysiology and Prognosis of Exercise-Induced Sustained Ventricular Tachycardia Associated with Healed Myocardial Infarction

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Of 150 consecutive patients with sustained monomorphic ventricular tachycardia (VT) (n = 116) or ventricular fibrillation (VF) (n = 34) late after acute myocardial infarction, 17 had reproduction of their sustained monomorphic VT during exercise testing. Data from these patients (group I) were compared with data from patients without exercise-induced VT (group II). No statistical difference was found between groups I and II with relation to age, sex, number of vessels with >70% stenosis, left ventricular ejection fraction, number of previous myocardial infarctions, inducibility during programmed stimulation and total mortality during follow-up. In group I, only 1 patient (6%) developed ST depression during exercise compared with 47 patients (35%) in group II (p <0.01). After a 34-month mean follow-up, 6 patients in group I (35%) and 18 patients in group II (13%) died suddenly (p = 0.02). It is concluded that sustained monomorphic VT is reproduced during exercise in only 11% of patients with spontaneous late sustained monomorphic VT or VF. Electrocardiographic findings do not support ischemia as a triggering mechanism of exercise-induced sustained monomorphic VT. Patients with exercise-induced sustained monomorphic VT have a high incidence of sudden death.

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In 1932 Wilson et al[1] described a type of ventricular tachycardia (VT) provoked by exertion. The underlying electrophysiologic mechanism of this arrhythmia can be speculative only because it is difficult to obtain such evidence in the intact human heart.[2–5] Three major mechanisms — reentry, abnormal automaticity or triggered activity — may be operative.[6–9] Our study reviews the incidence, possible mechanism and prognostic value of exercise-induced VT in patients with a healed myocardial infarct.

METHODS

Study patients: The study group consisted of 150 consecutive patients with an old myocardial infarction admitted to the Academic Hospital of Maastricht (115 patients) or Liège (35 patients) for the evaluation of a spontaneous occurrence of sustained monomorphic VT (116 patients) or ventricular fibrillation (VF) (34 patients). In each patient information included a complete history and physical examination, a left ventricular angiogram, coronary angiography, exercise testing and programmed electrical stimulation within a period of 3 months after the arrhythmic event.

Exercise test: In 114 patients exercise testing was performed on a motor-driven treadmill according to the Bruce protocol.[10] In the remaining patients, exercise electrocardiography was performed on a bicycle ergometer, in the upright position, with an initial load of 30 W and increased in steps of 30 W. Each load was maintained for a period of 3 minutes. Leads I, II, aVF, V_1, V_5 and V_6 were continuously monitored during and ≥5 minutes after exercise. Criteria for terminating exercise included: reaching 85% of the maximal age-predicted heart rate, occurrence of sustained VT or VF, and inability to perform further exercise because of limiting symptoms (angina, dyspnea and fatigue). The exercise tests were analyzed for presence of sustained VT/VF, ST-segment changes, exercise duration and maximal exercise heart rate. The test was considered positive for exercise-induced ischemia when ≥1 mm of flat or downsloping ST-segment depression occurred during exercise or recovery. In patients with exercise-induced sustained VT, the exercise test was repeated with antiarrhythmic therapy until a drug could be found to prevent the recurrence of the arrhythmia. Furthermore, a thallium exercise scan was performed in 41% of patients with and in 12% of patients without exercise-induced VT.

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TABLE I Clinical Characteristics

	Group I (n = 17)	Group II (n = 133)
Mean age (year)	62 ± 7	60 ± 9
Men/women	13 (76%)	114 (86%)
Location of myocardial infarct		
Anterior	8 (47%)	56 (42%)
Inferior	6 (35%)	49 (37%)
Both	3 (18%)	28 (21%)
Previous cardiac arrest	1 (6%)	33 (25%)
Angina class (III or IV)	2 (12%)	5 (4%)
Coronary bypass	1 (6%)	8 (6%)

Electrophysiologic study: Programmed electrical stimulation was performed in all patients with ≥ 2 electrodes introduced percutaneously from the femoral veins. One hundred two patients had a baseline study after discontinuation of antiarrhythmic drugs for ≥ 5 half-lives, 125 patients were studied while taking antiarrhythmic therapy, and in 77 patients the study was performed with and without drug therapy. Electrophysiologic study was performed with patients in the postabsorptive, nonsedated state, according to a previously described protocol.[11] Ventricular stimulation with up to 3 extrastimuli was performed for each patient from the right ventricular apex; no isoproterenol was given during the study. The choice for the best antiarrhythmic drug was based on clinical judgment and was not guided by invasive drug testing.

Coronary angiography: Selective coronary angiography was performed in multiple projections using the Judkin's technique.[12] Clinically important coronary artery disease was defined as $\geq 70\%$ narrowing of at least 1 major vessel or $\geq 50\%$ narrowing of the left main coronary artery. The distribution of disease was characterized according to the involvement of the left main, the left anterior descending, the left circumflex and the right coronary arteries. Left ventricular ejection fraction was assessed from the left ventricular angiogram in the right anterior oblique projection.

Follow-up: Long-term follow-up was obtained in all patients by outpatient clinic visits, records of hospital readmissions and follow-up by telephone. End points were death from any cause, sudden death and the nonfatal recurrence of the clinical arrhythmia.

Definitions: SUDDEN DEATH: Sudden death is..."natural death due to cardiac causes heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms, in an individual with or without known preexisting heart disease, but in whom the time and mode of death are unexpected."[13]

SUSTAINED VENTRICULAR TACHYCARDIA: This denotes VT lasting >30 seconds or requiring pharmacologic or electrical intervention, or both, because of circulatory collapse.

RECURRENCE OF CLINICAL ARRHYTHMIA: This denotes proved recurrence of sustained VT or VF after the first arrhythmic event.

Statistical analysis: Based on the results of exercise testing, 2 groups were formed: group I included 17 patients showing reproduction of their sustained VT during exercise, and group II (133 patients) without exercise-induced VT.

Continuous and discrete variables were compared between groups I and II by the Student's *t* test and the chi-square test, respectively. For 2 × 2 tables with cell frequencies of <5, analysis was performed using Fisher's exact test. Survival curves were compared using the log-rank test. Results are expressed in percentage or as mean ± SD. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics: Selected clinical characteristics and their percent occurrence in each group are listed in Table I. No statistical difference was found between groups I and II with relation to age, sex, location of previous myocardial infarction, previous cardiac arrest, angina class, and history of coronary artery bypass grafting before the clinical arrhythmia.

Exercise testing: During exercise testing, 17 patients (11%) developed sustained VT (Figure 1). None (group I) had chest pain or a positive thallium scan and only 1 (6%) had ST-segment depression, compared with 47 patients (35%) in group II ($p < 0.01$). Three (18%) and 26 (20%) patients had ST elevation in groups I and II, respectively. In group I, a good antiarrhythmic drug to prevent the recurrence of sustained VT during the exercise test was found in 95% of patients (amiodarone in 53%, sotalol in 35% and propafenone in 7%) and only 2 patients had nonsustained VT.

We analyzed the onset of sustained VT induced during exercise testing: 7 patients (41%) had sustained VT during the first 3 minutes of exercise (first stage) and 7 during the recovery period. All but 1 patient had exercise-induced sustained VT with a right bundle branch block pattern. Two patients had VF (without sustained VT) during exercise testing (1%) and they were included in group II. Both had ST depression and a positive thallium scan during exercise.

Angiographic characteristics: No statistical difference was found between the 2 groups concerning left ventricular ejection fraction, the presence of aneurysm and the extent of coronary artery disease.

Electrophysiologic features: In group I, thirteen patients (76%) were studied without drugs, 14 (82%) were studied while receiving oral antiarrhythmic drugs and 10 (59%) had both studies. No statistical difference was found between groups I and II with relation to the choice of antiarrhythmic drug (amiodarone 53 vs 56%, sotalol 35 vs 26% and propafenone 12 vs 16%). In 85% of group I and 82% of group II a sustained VT was inducible without drugs. With drugs, 71 and 70% in groups I and II, respectively, had induction of sustained VT.

Follow-up: After a 34-month mean follow-up (range 1 to 108), 7 patients in group I (41%) and 42 in group II (37%) had a nonfatal recurrence of their ventricular arrhythmia (p = not significant). Total mortality was 41% in group I and 26% in group II (p = not significant). Thirty-five percent of patients with exercise-induced sustained VT died suddenly during follow-up (3 taking amiodarone, 2 taking sotalol and 1 propafenone) compared with 14% in group II (p = 0.02) (Figure 2). In group I all 6 patients who died suddenly had hemodynamically unstable exercise-induced sustained VT compared with only 2 of 11 patients not dying suddenly (p = 0.002). The 2 patients with VF and proved ischemia during exercise testing underwent coronary artery bypass grafting, and they are alive after a follow-up of 34 and 60 months, respectively.

DISCUSSION

Incidence of exercise-induced ventricular tachyarrhythmia: Whereas extensive attention has been given in published reports to the usefulness of exercise stress testing to expose and to treat disorders in ventricular rhythm disturbances,[14,15] few reports have documented the incidence of exercise-induced ventricular tachyarrhythmias in patients with spontaneous sustained ventricular arrhythmias.[16] Recently, Young et al[16] reviewed the incidence of sustained VT/VF during symptom-limited exercise in 263 patients with a history of sustained VT/VF, including 62% of patients with coronary artery disease. Sustained VT/VF was noted in 23 patients (9%). Our data are in agreement with these findings. We found an incidence of 13% of exercise-induced sustained VT/VF. As also reported by Young et al,[16] no complications occurred during restoration of sinus rhythm (by direct-current shock, intravenous medication, and so forth).

Mechanism of exercise-induced ventricular tachyarrhythmia: As stressed by Coumel et al,[17] 3 components having a close interrelation are usually needed to elicit a spontaneous arrhythmia: (1) a substrate (e.g., a scar after myocardial infarction); (2) an initiating factor (e.g., a premature beat); and (3) modulating factors (like nervous control). By increasing myocardial oxygen demand, exercise testing can induce myocardial ischemia and potentially trigger the onset of a ventricular tachyarrhythmia.[7] This was probably the mechanism in our 2 patients with exercise-induced VF associated with significant ST depression and chest pain. Electrocardiographic and thallium findings in our study, however, do not support the hypothesis that this mechanism can be implicated in the genesis of sustained VT during exercise. In fact only 1 patient in this group had significant ST depression.

In most patients in groups I and II, sustained VT could be initiated during programmed electrical stimulation supporting reentry as the underlying mecha-

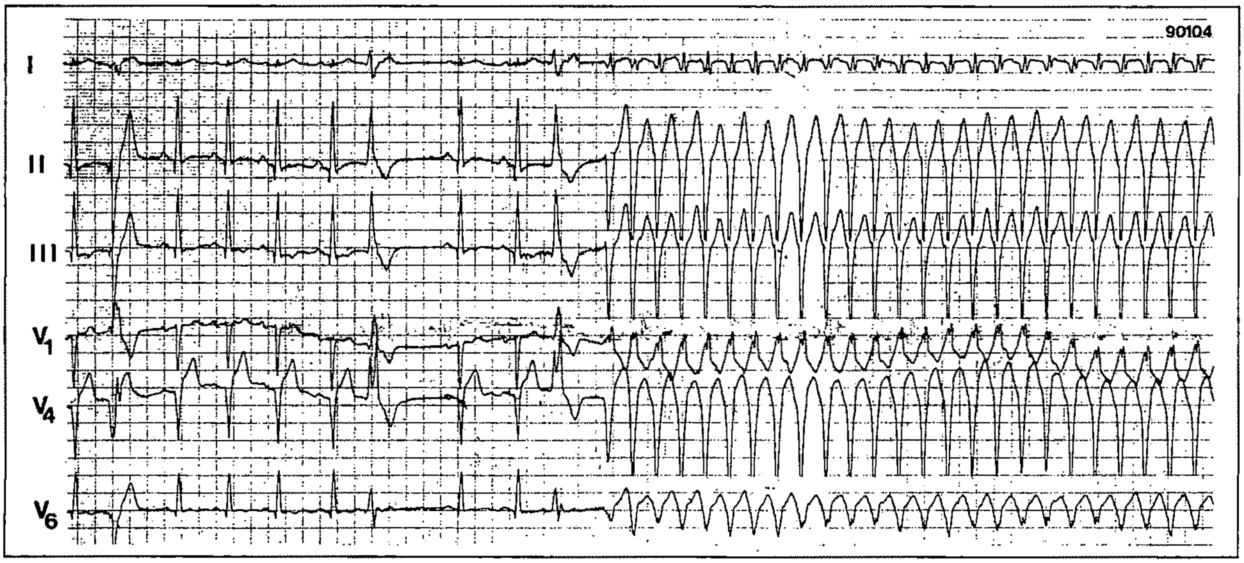

FIGURE 1. Onset of ventricular tachycardia during the recovery period of treadmill exercise testing in a 61-year-old man.

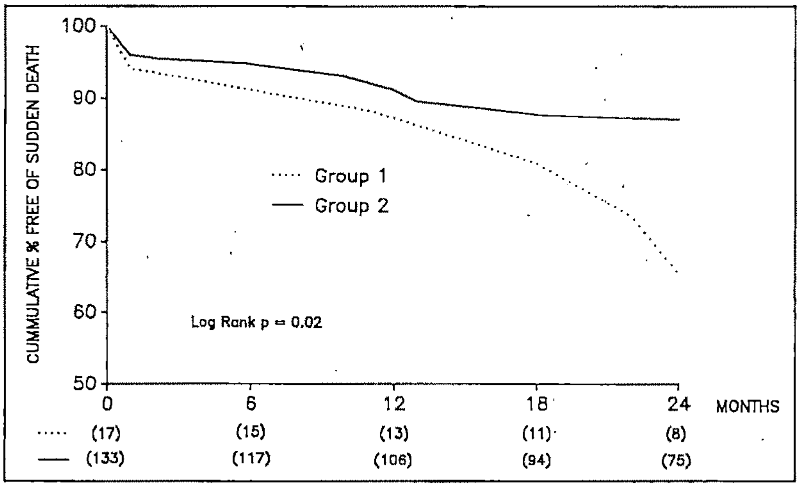

FIGURE 2. Two-year cumulative percentage free of sudden death. *Numbers in parentheses* indicate the number of patients still in follow-up at the beginning of a given interval. Group 1 = patients with exercise-induced sustained ventricular tachycardia; Group 2 = patients without exercise-induced sustained ventricular tachycardia.

nism.[18] It is tempting to speculate that modification in duration of refractory period and conduction velocity induced by changes in autonomic balance occurring during or shortly after exercise played a role in the initiation and maintenance of reentry. As reported by Pratt et al,[19] in patients with a diseased heart, a relatively small change in the autonomic nervous tone can elicit important changes in refractory period and in cell membrane conductivity compared with normal muscle. This can explain why in 82% of our population exercise-induced sustained VT occurred during a relatively small effort (first stage) or during the recovery period.

Prognostic significance of exercise-induced ventricular tachyarrhythmias: The prognostic value of ventricular premature beats after myocardial infarction on Holter monitoring is well recognized.[20] However, the prognostic significance of exercise-induced ventricular arrhythmias is more controversial. Sami et al[21] retrospectively examined the prognostic significance of exercise-induced ventricular arrhythmia in 1,486 patients with stable coronary artery disease included in the Coronary Artery Surgery Study registry. The 5-year incidence of cardiac death was similar, in patients with and without exercise-induced ventricular arrhythmia. Similarly findings were published by Nair et al[22] after a mean follow-up of 47 months and by other investigators.[8,23,24] In contrast, Califf et al[25] showed in a population with significant coronary artery disease and angina that ventricular premature beats induced by exercise are an independent prognostic factor.

In our study we included only patients who had spontaneous episodes of sustained VT or VF. A high incidence of sudden death during follow-up (35%) was found in patients with exercise-induced sustained VT. The difference between the prognostic significance of exercise-induced ventricular arrhythmia in our study compared with previously reported reports may be explained by 2 factors: (1) Our population is highly selected, all patients having a history of myocardial infarction and sustained VT/VF before the exercise test. (2) In other studies, no distinction was make between "simple ventricular premature beats" and "complex ventricular premature beats" (including sustained VT).

Clinical implications: Patients with old myocardial infarction and exercise-induced hemodynamically unstable sustained VT have a high incidence of sudden death during follow-up. In this highly selected subgroup of patients, the noninducibility of sustained VT during exercise testing while taking antiarrhythmic drug therapy was not predictive of a good outcome. This suggests that this subgroup requires an aggressive approach (arrhythmia surgery, automatic implantable cardioverter defibrillator, and so forth). Furthermore, even if the probable underlying mechanism is reentry in myocardium highly sensitive to small changes in autonomic balance, β blockers or medication with a significant β-adrenergic effect (e.g., propafenone) may not be completely protective or may be contraindicated in other patients (poor left ventricular function).

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Clinical and Electrophysiologic Effects of Magnesium Sulfate on Paroxysmal Supraventricular Tachycardia and Comparison with Adenosine Triphosphate

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Electrophysiologic studies have shown that intravenous magnesium sulfate prolongs atrioventricular (AV) nodal conduction and refractoriness and thus could play a role in the management of patients with paroxysmal AV reentrant supraventricular tachycardia (SVT). The present study evaluates the clinical and electrophysiologic effects of intravenous magnesium sulfate in patients with SVT and compares them with those of adenosine triphosphate (ATP), one of the most potent drugs in the treatment of this arrhythmia. Patients with inducible sustained SVT were treated with ATP (10 or 20 mg) and magnesium sulfate (2 g over 15 seconds) during electrophysiologic study. If the tachycardia failed to terminate by the sixth minute, an additional 2 g dose of magnesium was given. ATP (10 or 20 mg) was significantly better than magnesium for terminating induced tachycardias (14 of 14 vs 6 of 14, p <0.0001). Arrhythmia termination with ATP was due to anterograde AV nodal blockade in all but 1 patient who developed retrograde block over an accessory pathway with decremental conduction. Arrhythmia termination by magnesium was due to retrograde block over an accessory pathway in 3 patients (including the patient with accessory pathway exhibiting decremental conduction), anterograde AV nodal conduction block in 2 patients and premature ventricular complexes in 1 patient. During induced tachycardias, only AH intervals were prolonged by ATP, whereas magnesium significantly prolonged AH and QRS intervals. Short-lasting side effects (chest pain, flushing, nausea) occurred after both drugs were administered but were more severe after magnesium.

In conclusion, there seems to be little role for the clinical use of intravenous magnesium sulfate for terminating SVT. The electrophysiologic effects of magnesium sulfate are more complex than previously believed. Magnesium sulfate may block retrograde conduction in accessory pathways.

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There has been a recent regain of interest in the antiarrhythmic effects of magnesium sulfate, a drug that was empirically used for years in the treatment of various types of cardiac arrhythmias.[1-4] Electrophysiologic studies have shown that magnesium significantly prolongs conduction time and refractoriness at the atrioventricular (AV) nodal level, without significantly affecting sinus cycle length or infranodal conduction.[2-4] Such properties, which resemble those of calcium channel blockers,[5] have prompted the initiation of clinical studies on the electrophysiologic effects of intravenous magnesium in patients with paroxysmal supraventricular tachycardia (SVT) due to a reentrant mechanism involving the AV node. Two such trials have been published so far but reported conflicting results.[6,7] The aim of the present study was twofold: (1) to further evaluate the clinical and electrophysiologic effects of intravenous magnesium sulfate in patients with SVT; and (2) to compare these effects with those of adenosine triphosphate (ATP), one of the most potent drugs for the acute management of SVT, known for its specific actions on the AV node.[8,9] Because of the ultrashort half-life of ATP,[10,11] we were able to compare the effects of both drugs, in each patient, during a single electrophysiologic study.

METHODS

Patients: The study group consisted of 15 consecutive patients (mean age 37 ± 15 years) who underwent electrophysiologic study in our laboratory for documented, recurrent SVT and who fulfilled the following criteria: (1) inducible sustained (≥10 minutes) orthodromic AV reentry tachycardia or AV nodal reentry tachycardia; (2) good hemodynamic tolerance of the induced SVT; and (3) no contraindication to the administration of magnesium sulfate (renal failure, hypocalcemia or blood pressure <90 mm Hg) (Table I). One patient with bronchial asthma, a known contraindication for ATP, received only magnesium sulfate. Two patients (nos. 5 and 6) had moderate left ventricular dysfunction related to long standing incessant SVT or coronary artery disease. The remaining patients had no demonstrable heart disease.

Electrophysiologic studies: Electrophysiologic studies were performed with the patients in the fasting, nonsedated state, after informed written consent had been obtained and using previously described techniques and protocol.[9] The study protocol was approved by the hospital committee on human research. All drugs were discontinued for ≥5 half-lives before the study. No patient had received amiodarone or drugs known to interfere

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TABLE I Clinical Characteristics and Control Electrophysiologic Data

Pt. No.	Age (yr) & Sex	SVT Mechanism–AP Location	AVNB (ms)	VPCLB (ms)
1	26F	AVR–left lateral	—	<260
2	36M	AVR–left lateral	—	<250
3	47F	AVR–left posterolateral	—	<300
4	44M	AVR–posteroseptal (C)	—	290
5	42F	Incessant AVR–posteroseptal (C)*	—	330
6	55M	AVR–left lateral	—	≤245
7	19M	AVR–left lateral (C)	<300	215
8	31F	AVR–left lateral (C)	≤235	≤290
9	56M	AVR–posteroseptal (C)	330	270
10	20F	AVR–left posterolateral (I)	275	≤250
11	17M	AVR–left lateral	—	210
12	36M	AVR–left lateral	≤230	≤265
13	61M	AVNR	330	325
14	50F	AVNR	310	—
15	22M	AVNR	370	310

*Accessory pathway with decremental conduction properties.

AP = accessory pathway; AVNB = atrial-paced cycle length that resulted in second-degree atrioventricular nodal block; AVNR = atrioventricular nodal reentry tachycardia; AVR = atrioventricular reentry tachycardia; C = concealed; I = intermittent; VPCLB = ventricular-paced cycle length that resulted in second-degree ventriculoatrial block in the atrioventricular node or in the accessory pathway in patients with atrioventricular nodal reentry or atrioventricular reentry, respectively; — = no information available.

with the metabolism of ATP (diazepam, aminophylline, dipyridamole). Tracings were recorded at a paper speed of 100 mm/s. Accuracy of measurements was ± 5 ms.

Definitions: Arrhythmia mechanisms were determined on the basis of retrograde atrial activation patterns and responses to cardiac stimulation. AV nodal reentry and AV reentry were diagnosed by standard criteria detailed elsewhere.[9] Since the earliest area of retrograde atrial activity during SVT is frequently difficult to determine accurately in patients with AV nodal reentry and in those with septal accessory pathways, we elected to measure retrograde conduction time (ventriculoatrial [VA] interval) from the earliest ventricular activity to the high right atrial electrogram in all patients.

Protocol and drug administration: ATP and magnesium sulfate were administered into the right femoral vein. ATP (available as ampules of 2 ml containing 20 mg ATP; Striadyne®, Wyeth Laboratories, France) was injected very quickly (within 1 second) and followed by saline flushing. Magnesium sulfate was administered as a 4 g/dl solution.

During control electrophysiologic study, the characteristics of anterograde and retrograde AV conduction were assessed along with the modes of induction and termination of SVT. During this evaluation, SVT did not terminate spontaneously and, by protocol design, was sustained for ≥10 minutes. After completion of the control electrophysiologic study, sinus rhythm was restored for a few minutes. SVT was subsequently reinduced with programmed cardiac stimulation and allowed to continue for 5 minutes without any intervention. An initial dose of 10 mg of ATP was then administered. If the tachycardia did not terminate within 1 minute after the 10 mg dose of ATP, a dose of 20 mg was then given. After a resting period of 5 minutes during which the patient was in sinus rhythm, SVT was reinduced by cardiac stimulation and allowed to continue for 5 minutes. Two grams of magnesium sulfate were then administered over a period of 15 seconds. If the tachycardia did not terminate within 6 minutes after completion of this injection, an additional 2 g dose of magnesium sulfate was given. Blood pressure was measured every 3 minutes.

Magnesium serum levels: Magnesium serum levels, as well as calcium, sodium and potassium levels, were determined after completion of the control electrophysiologic study during sinus rhythm and after 5 minutes of induced sustained SVT before magnesium administration. Repeated measurements were performed at 3-minute intervals during the 12 minutes following the initial drug administration. Serum magnesium levels were determined by atomic absorption (Perkin-Elmer 305A).

Data analysis: The timing and mode of tachycardia termination, the effects of drugs on electrophysiologic parameters and side effects were noted in all patients. Each patient served as his own control. Comparisons were made by means of Student's paired *t* test and Fisher's exact test. Data were expressed as mean ± standard deviation and a p value <0.05 was considered significant.

RESULTS

Electrophysiologic control data (Table I): The mechanism of SVT was AV reentry and AV nodal reentry in 12 and 3 patients, respectively. One patient (no. 5) had almost incessant AV reentrant tachycardia with RP > PR related to a posteroseptal pathway exhibiting AV node-like properties. This was the only patient with AV reentry who exhibited decremental conduction during ventricular pacing. In the 3 patients with AV nodal reentrant tachycardia, the mechanism of SVT was of the common "slow-fast" type. Cycle lengths of induced SVT measured before administration of ATP and magnesium sulfate in the 14 patients given both drugs were similar (355 ± 65 ms vs 350 ± 63 ms, p = not significant) (Tables II and III).

Effects of adenosine triphosphate (Table III): All 14 patients who received ATP responded with termination of induced SVT: 13 patients responded to the 10 mg dose, and 1 required 20 mg. Termination of SVT occurred 9 to 29 seconds (mean 19 ± 6) after ATP administration. In 13 of 14 patients the rentrant circuit of SVT was broken by block of anterograde conduction in the AV node following prolongation of the AH interval in 12 patients (Figure 1). This was not associated with any change in HV, QRS or VA intervals. In Patient 5, SVT terminated because of retrograde block in the accessory pathway after marked VA prolongation.

The interval from the last retrograde atrial activity during SVT to the first post-tachycardia sinoatrial complex ranged from 730 to 1,400 ms (mean 948 ± 222). The longest sinus rhythm cycle length after SVT termination ranged from 500 to 1,850 ms (mean 1,105 ± 551). Transient second- or high-degree AV block (lasting 1 to 6 seconds) were observed in 4 patients after SVT termination. Atrial or ventricular premature complexes, or both, were noted in 9 patients within the first minute after SVT termination. Immediate (within 1 minute) spontaneous recurrence of sustained AV nodal or AV reentrant tachycardia occurred in 1 and 2 patients, respectively, including the patient with incessant AV reentry. The observed arrhythmias were well tolerated.

EFFECTS OF MAGNESIUM SULFATE (TABLE III): Two grams of magnesium sulfate terminated SVT in 6 of the 15 patients within 2 to 70 seconds (mean 40 ± 29). None of the 9 patients in which a 2 g dose failed to terminate SVT had their tachycardia terminated by the additional bolus of 2 g of magnesium sulfate given 6 minutes later.

TERMINATION OF SUPRAVENTRICULAR TACHYCARDIA BY MAGNESIUM SULFATE: In 2 patients (nos. 11 and 14), SVT terminated because of block of anterograde conduction in the AV node 70 and 45 seconds, respectively, after completion of drug administration. In Patient 11 transient AH alternans occurred, whereas in patient 14

TABLE II Electrophysiologic Effects of Adenosine Triphosphate on Paroxysmal Supraventricular Tachycardia*

	Before Drug (ms)				After Drug (ms)				SVT Termination	
Pt. No.	CL	AH	VA	HV	CL	AH	VA	HV	Mode	Time (sec)
1	260	80	140	40	285	105	140	40	AG-AVN	12
2	290	90	150	50	290	90	150	50	AG-AVN	22
3	345	125	180	40	380	160	180	40	AG-AVN	17
4	350	50	240	60	380	80	240	60	AG-AVN	28
5	500	110	350	40	560	110	410	40	RB-AP	17
6	335	95	190	50	385	145	190	50	AG-AVN	18
7	310	60	200	50	355	105	200	50	AG-AVN	16
8	325	105	180	40	350	130	180	40	AG-AVN	9
9	370	180	150	40	410	220	150	40	AG-AVN	19
11	335	110	185	40	380	155	185	40	AG-AVN	20
12	355	150	170	35	420	215	170	35	AG-AVN	29
13	340	225	65	50	385	270	65	50	AG-AVN	27
14	375	290	50	35	435	350	50	35	AG-AVN	20
15	480	415	25	40	525	460	25	40	No	
15 (20 mg)	465	400	25	40	565	500	25	40	AG-AVN	14

*Results obtained with 10 mg of adenosine triphosphate (ATP) (for patient 15 who did not respond to 10 mg of ATP the effects of a 20 mg dose are also shown; patient 10 did not receive ATP because of asthma).

AG-AVN = anterograde block in the atrioventricular node; AH = interval from the onset of the atrial deflection to the His bundle activity in the His bundle lead; CL = cycle length; HV = interval from the onset of His bundle activity to the earliest deflection of the QRS complex; RB-AP = retrograde block in the accessory pathway; Time = time from the end of drug injection to supraventricular tachycardia termination; SVT = supraventricular tachycardia; VA = interval from the earliest deflection of the QRS complex to the onset of atrial activity recorded at the high right atrium.

TABLE III Electrophysiologic Effects of Magnesium Sulfate on Paroxysmal Supraventricular Tachycardia

		Before Drug (ms)					After Drug (ms)					SVT Termination	
Pt. No.	D (g)	CL	AH	VA	HV	QRS	CL	AH	VA	HV	QRS	Mode	Time (sec)
1	2	265	85	140	40	75	290	110	140	40	80	No	—
	4	285	105	140	40	75	310	130	140	40	80	No	—
2	2	290	90	150	50	120	295	95	150	50	125	RB-AP	2
3	2	335	115	175	45	120	350	130	175	45	125	No	—
	4	350	130	175	45	120	385	165	175	45	125	No	—
4	2	350	70	235	50	155	390	100	250	50	165	No	—
	4	365	80	235	50	155	375	85	240	50	160	No	—
5	2	510	110	360	40	75	605	110	455	40	80	RB-AP	48
6	2	330	90	190	50	65	350	85	215	50	70	RB-AP	8
7	2	320	70	200	50	80	320	70	200	50	85	No	—
	4	320	70	200	50	80	320	70	200	50	80	No	—
8	2	330	120	170	40	70	355	135	180	40	75	VPCs	68
9	2	360	170	150	40	70	420	220	160	40	70	No	—
	4	380	185	150	45	70	430	215	160	50	70	No	—
10	2	315	55	210	40	70	355	95	220	40	75	No	—
	4	350	100	210	40	70	355	100	215	40	75	No	—
11	2	325	100	185	40	65	330	105	185	40	65	AG-AVN	70
12	2	350	145	170	35	70	400	185	175	35	75	No	—
	4	360	155	170	35	70	390	175	175	35	75	No	—
13	2	330	215	65	50	80	350	230	70	50	85	No	—
	4	345	230	65	50	80	360	245	70	60	85	No	—
14	2	350	265	50	35	75	465	380	50	35	80	AG-AVN	45
15	2	460	385	25	50	70	470	395	25	50	70	No	—
	4	470	395	25	50	70	520	445	25	50	75	No	—

D = cumulative dose of magnesium sulfate administered; VPCs = ventricular premature complexes; other abbreviations as in Table II.

AH interval progressively increased before tachycardia termination. In Patient 11, SVT recurred within a few seconds, triggered by 1 ventricular premature beat. An additional 2 g dose of magnesium sulfate was administered at the sixth minute and resulted in tachycardia termination by an identical mechanism.

In 3 patients with AV reentry tachycardia (patients 2, 5 and 6), SVT terminated due to block of retrograde conduction in the accessory pathway.

In patient 2, retrograde block over the accessory pathway occurred 2 seconds after completion of magnesium infusion. No change in VA interval was observed before SVT termination (Figure 2). Repeated attempts to reinduce SVT during the 5 minutes that followed its termination by magnesium sulfate were unsuccessful because of altered retrograde conduction in the accessory pathway. This contrasted with the easy induction of SVT before drug administration. Eventually, nonsus-

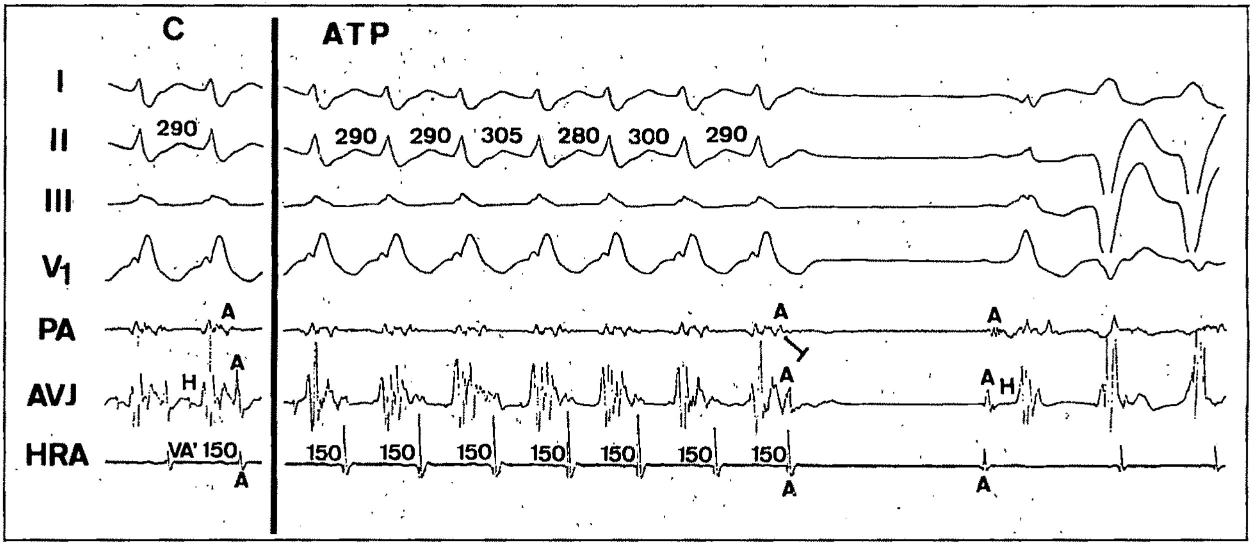

FIGURE 1. Termination of atrioventricular reentrant tachycardia after administration of 10 mg of adenosine triphosphate (ATP) in patient 2 with an overt left lateral accessory pathway. Electrocardiographic leads I, II, III and V_1 are shown, as well as electrograms from the pulmonary artery trunk (PA), atrioventricular junction (AVJ) and high right atrium (HRA). During control (C), the earliest retrograde atrial activation is recorded on the pulmonary artery electrogram; the tachycardia cycle length and the retrograde conduction time (VA) are 290 and 150 ms, respectively. Twenty-two seconds after the rapid intravenous administration of 10 mg of ATP, atrioventricular reentrant tachycardia is terminated because of the development of anterograde conduction block in the atrioventricular node. Note a slight AH alternance before tachycardia termination without change in the retrograde conduction time after ATP administration. Also note 2 premature ventricular complexes following the first sinus preexcited complex after tachycardia termination.

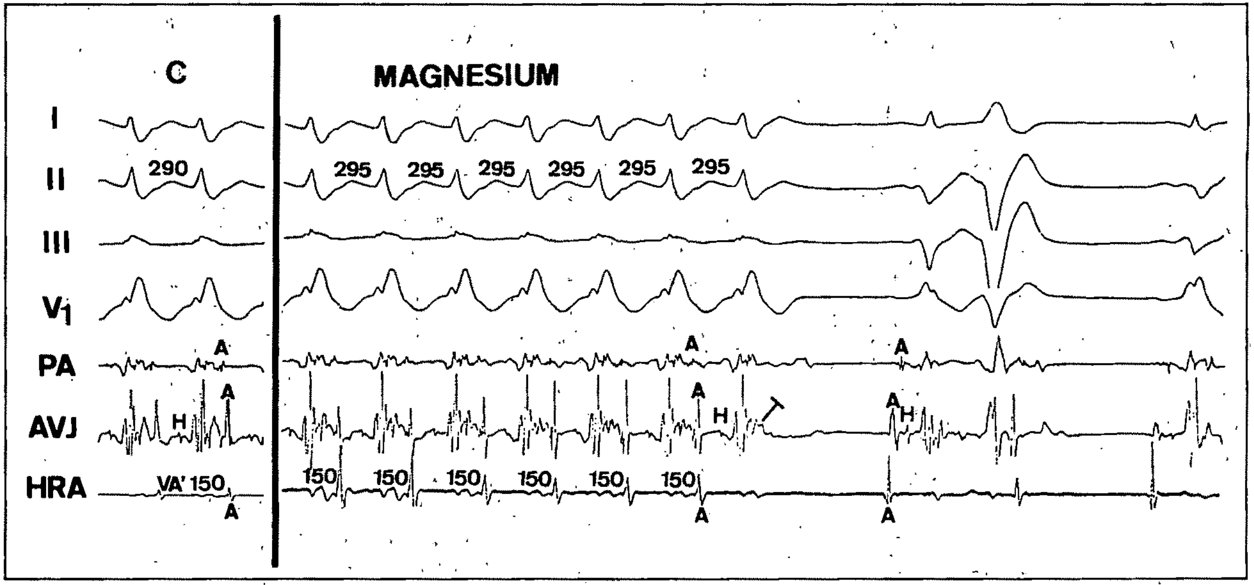

FIGURE 2. Termination of atrioventricular reentrant tachycardia after administration of 2 g of magnesium sulfate in the same patient as in Figure 1. During control (C), tachycardia cycle length and ventriculoatrial (VA) interval are 290 and 150 ms, respectively. Two seconds after completion of intravenous administration of 2 g of magnesium sulfate, tachycardia is terminated because of the development of retrograde conduction block in the accessory pathway. Note that the cycle length of the tachycardia slightly increases (by 5 ms) because of AH prolongation; however, no change in retrograde conduction is observed. Also note that the first sinus complex after tachycardia termination most probably exhibits some degree of fusion with a premature ventricular complex. Abbreviations as in Figure 1.

TABLE IV Comparative Efficacy and Electrophysiologic Effects of Adenosine Triphosphate and Magnesium Sulfate on Paroxysmal Supraventricular Tachycardia in 14 Patients

	ATP	Magnesium	p Value
Overall SVT termination	14	6	<0.001
Mode of termination of SVT			
AV nodal block	13	2	<0.00005
Block in accessory pathway	1	3	NS
Triggered by VPCs	0	1	NS
Time of tachycardia conversion(s)	18 ± 5	40 ± 29	NS
After conversion of SVT			
Interval AA (ms) (n = 5)*	1,017 ± 276	824 ± 192	NS
Interval AA max (ms) (n = 4)*	1,297 ± 851	652 ± 144	NS
Transient ≥ 2nd AV block	4	0	<0.05
APCs, VPCs	9	3	<0.05
Recurrent spontaneous SVT	3	2	NS

*Number of patients for whom both data with adenosine triphosphate and magnesium were available for comparison (for data on AA and AA max of all 15 patients, see text).

AA = interval from the last retrograde atrial activity during supraventricular tachycardia to the first post-tachycardia sinoatrial complex; AA max = longest sinus rhythm cycle length after termination of tachycardia; APCs = atrial premature complexes; AV = atrioventricular; NS = not significant; other abbreviations as in Table II.

tained SVT was reinduced 6 minutes after its termination by magnesium; this tachycardia exhibited transient left bundle branch block and terminated spontaneously 15 seconds later, again because of retrograde block over the accessory pathway. This sequence of events occurred once again 1 minute later, with a third episode of induced SVT terminating again by retrograde block over the accessory pathway.

In patient 6, retrograde block over the accessory pathway was observed 8 seconds after completion of the magnesium infusion. No significant change in VA interval could be noted on the last 10 complexes of SVT. About 2 minutes after tachycardia termination, the ventricular pacing cycle length inducing retrograde block in the accessory pathway was 200 ms longer than the control value (440 vs 240 ms). AV reentrant tachycardia was reinduced 1 minute later but was nonsustained, terminating after 8 beats, again owing to retrograde block over the accessory pathway.

In patient 5, progressive marked VA prolongation (from 360 to 455 ms) preceded tachycardia termination due to retrograde block in the accessory pathway 48 seconds after completion of magnesium infusion.

In 1 patient (no. 8), termination of AV reentrant tachycardia was triggered by ventricular ectopy. Rare spontaneous ventricular premature complexes were observed during sinus rhythm and during induced SVT. After administration of magnesium sulfate, however, a marked increase in ventricular ectopic activity occurred until a ventricular triplet terminated SVT 68 seconds drug administration. SVT was reinduced and no ventricular ectopic activity was observed during the next 5 minutes until a second 2 g dose of magnesium sulfate was administered: this resulted in numerous ventricular premature complexes and eventual arrhythmia termination by a ventricular couplet 2 minutes after the second injection.

ELECTROPHYSIOLOGIC EFFECTS OF MAGNESIUM DURING SUPRAVENTRICULAR TACHYCARDIA: In 15 patients, the maximal effects of 2 g magnesium sulfate on tachycardia cycle length, AH, HV, QRS and VA intervals were determined during SVT. Tachycardia cycle length increased from 348 ± 61 ms to 383 ± 82 ms ($p = 0.001$). AH increased from 139 ± 89 ms to 163 ± 103 ms ($p < 0.01$). QRS increased from 84 ± 26 ms to 88 ± 28 ms ($p < 0.0001$). VA also increased from 165 ± 81 ms to 177 ± 100 ms, but the change did not reach statistical significance ($p = 0.08$). In contrast, HV interval was not altered by magnesium (44 ± 6 ms before and after magnesium). No electrophysiologic features in the drug-free state, namely anterograde AV conduction over the AV node or retrograde conduction over the AV node or the accessory pathway in patients with AV nodal and AV reentrant tachycardia, respectively, distinguished patients whose tachycardias responded to magnesium from those who did not (Table I).

ELECTROPHYSIOLOGIC EFFECTS OF MAGNESIUM AFTER SUPRAVENTRICULAR TACHYCARDIA TERMINATION (TABLE IV): The interval from the last retrograde atrial activity during SVT to the first post-tachycardia sinoatrial complex ranged from 570 to 1,100 ms (mean 824 ± 192, n = 5). The longest sinus rhythm cycle length after SVT termination ranged from 500 to 830 ms (mean 652 ± 144, n = 4). Atrial or ventricular premature complexes, or both, were noted in 3 patients within the first minute after tachycardia termination. Sustained spontaneous SVT recurred in 2 patients, including the patient with incessant AV reentry. Preexcitation remained present in all patients with anterogradely conducting accessory pathways.

Comparative efficacy and electrophysiologic effects of adenosine triphosphate and magnesium sulfate: In the 14 patients who received both ATP and magnesium sulfate during induced SVT, the overall efficacy of ATP (10 or 20 mg) was significantly higher than that of 2 g of magnesium sulfate (14 of 14 vs 6 of 14; $p < 0.0001$). The efficacy of ATP continued to be significantly higher if only the 10 mg dose of ATP was considered (13 of 14 vs 6 of 14 $p < 0.001$) or if recurrence of SVT during the immediate period following tachycardia termination was counted as drug failure (11 of 14 vs 4 of 14; $p < 0.05$). The most pertinent electrophysiologic effects of ATP and magnesium are compared in 14 patients in Table IV.

Comparison of adverse effects: Similar adverse effects (flushing, nausea, headache) occurred almost invariably after administration of both ATP and magnesium sulfate, but were more severe after magnesium. However, all adverse effects were short-lasting, with complete disappearance within 1 minute of ATP injection and within 2 to 3 minutes of magnesium administration. Clinically significant hypotension was not seen and no interventions were required because of adverse effects.

Magnesium serum levels: Magnesium serum levels during sinus rhythm and during induced sustained SVT before magnesium administration were within normal range (1.7 to 2.4 mg/dl) in all but 3 patients with borderline low (patients 7 and 11) or borderline high (patient 2) levels. Two of the 6 patients with SVT responding to 2 g of magnesium sulfate nevertheless received a second 2 g dose (because of SVT recurrence or unexpected response). Thus, 11 patients received a total of 4 g. In the 4 patients who received a single 2 g dose of magnesium sulfate, the highest serum magnesium level was recorded 3 minutes after injection and ranged from 4 to 5.2 mg/dl (mean 4.5 ± 0.5). In the 11 patients who received a second 2 g dose of sulfate magnesium at the sixth minute, the highest serum magnesium level ranged from 3.4 to 7.5 mg/dl (mean 5.2 ± 1.5) and peaked at the ninth and twelfth minute in 10 and 1 patients, respectively. Maximal magnesium serum levels achieved in patients not responding to 2 g of magnesium (patients who received an additional dose of 2 g of magnesium by protocol design) were not significantly different from the levels recorded at the time of arrhythmia termination in responders (5.2 ± 1.9 vs 3.4 ± 1.1 mg/dl, $p = 0.1$) or from the maximal levels measured in patients who responded to 2 g of magnesium (5.2 ± 1.9 vs 4.2 ± 0.7 g/dl, $p = 0.26$). Serum levels of sodium, potassium and calcium were within normal limits and did not vary significantly throughout the study.

DISCUSSION

This is the first comparative study of the clinical and electrophysiologic effects of magnesium sulfate and ATP on SVT. The consistent application of ATP before magnesium sulfate in every patient, required by study design, is unlikely to have created a bias owing to the ultrashort half-life of ATP (<10 seconds)[10,11] and the fact that cycle lengths and other electrophysiologic parameters during SVT were almost identical before administration of ATP and magnesium.

Efficacy of magnesium sulfate: In the present study, tachycardias in 6 of 15 patients (40%) were terminated by a dose of 2 g of magnesium sulfate, whereas none of the remaining 9 patients responded to an additional bolus of 2 g of magnesium sulfate given 6 minutes later. Such a relatively low efficacy rate appears intermediate between the results of the only 2 studies on the effects of magnesium sulfate on SVT published to date.[6,7] Wesley et al[6] reported termination of SVT in 7 of 10 patients (70%), whereas Sager et al[7] reported termination of tachycardia in only 2 of 11 patients (18%). The most likely explanation for these different results could be found in the different modes of drug administration: Wesley et al[6] administered 2 g of magnesium sulfate as a rapid intravenous bolus of a highly concentrated solution (4 ml of a 50 g/dl solution over 5 seconds). In contrast, Sager et al[7] gave the same amount of magnesium as a slow intravenous infusion over 10 minutes. In our study, we elected to administer the drug as a bolus of 50 ml of a 4 g/dl solution over 15 seconds.

Magnesium serum levels measured at the time of conversion in patients responding to magnesium were also achieved in patients who received the double dose of magnesium because of arrhythmia persistence. In addition, no obvious electrophysiologic features in the drug-free state distinguished patients who responded to magnesium from those who did not (with the exception of patient 5, see later). Therefore, other parameters must have played a role in arrhythmia conversion. Magnesium concentration in mononuclear blood cells were not measured in our patients. Such magnesium levels have been found to reflect the cations concentration in cardiac muscle more accurately than magnesium serum levels in some[12] but not in all studies.[13]

Efficacy and side effects: magnesium sulfate versus adenosine triphosphate: Of the 14 patients who received both ATP and magnesium sulfate, all responded to ATP but only 6 (43%) responded to magnesium sulfate ($p < 0.0001$). The high efficacy rate of ATP (and especially of the 10 mg dose) in converting SVT is consistent with the results of previous studies published by our group[9] and others.[14,15] It is possible that higher doses or more rapid administration of magnesium sulfate[6] would have resulted in higher arrhythmia conversion rates. However, because of the adverse effects observed with magnesium sulfate in our study, which were frequently intolerable and invariably more prolonged and marked than those observed after ATP, we would be reluctant to recommend a more aggressive protocol of drug administration.

Mode of tachycardia termination: magnesium sulfate versus adenosine triphosphate: ATP terminated SVT by blocking anterograde conduction over the AV node in all patients but 1, in whom tachycardia terminated because of block in an accessory pathway with AV node-like properties. AV nodal blockade is the mode of tachycardia termination consistently reported with ATP.[8,9]

In considering the reported electrophysiologic properties of magnesium sulfate,[2-4] one would have expected this drug to terminate SVT in a way similar to that with ATP, i.e., mainly by blocking conduction in the AV node. However, the mode of tachycardia termination by magnesium sulfate observed in our study was more heterogeneous. Although tachycardia was interrupted after AV nodal blockade in 2 of 6 patients, retrograde block in an accessory pathway was the mechanism of tachycardia termination in 3 patients. In 1 of our patients (no. 5), such a mode of termination could be expected because of the AV node-like properties of the patient's concealed posteroseptal accessory pathway. Retrograde conduction block over accessory pathways with AV node-like properties has also been described with adenosine[16] and verapamil,[17] and was also observed with ATP in this patient. However, in the other 2 patients (nos.

2 and 6), magnesium-induced block of conduction surprisingly occurred in accessory pathways that had no decremental properties or no long refractory period in the drug-free state. That retrograde block in the accessory pathway was not coincidental but related to magnesium sulfate administration in these 2 patients is supported by the transient impairment of retrograde conduction following magnesium administration as well as by the reproducible character of the results, with the repeated termination of subsequently induced AV reentrant tachycardia by a retrograde block in the accessory pathway. Lack of AH alternans before tachycardia termination makes a functional block in the accessory pathway caused by AV nodal alternating conduction[17] an unlikely explanation of the mechanism of tachycardia termination in these 2 patients. A direct depressive effect of magnesium sulfate on the accessory pathways thus appears to be the most plausible explanation. The exact electrophysiologic mechanism by which magnesium sulfate exerts this depressive action is unclear. However, such an effect, associated with the observed slight widening of the QRS complex in most patients, suggests that an action on slow channel current is unlikely to be the only operative mechanism of magnesium, at least at the dose and injection rate used in our study. DiCarlo et al[2] reported that infusion of 6 g of magnesium sulfate over 6 minutes had a small but statistically significant effect on intraventricular conduction during rapid ventricular pacing but not during sinus rhythm. In addition, magnesium sulfate has been found to slow[18,19] and terminate[18] sustained monomorphic ventricular tachycardia in selected cases. Such findings actually support the view that the mechanism of action of magnesium sulfate is more complex than previously believed.

A third mode of tachycardia termination by magnesium sulfate was repeatedly observed in 1 of our patients whose AV reentrant tachycardia was terminated twice: by a ventricular triplet after an initial dose of 2 g of magnesium sulfate and by a ventricular couplet after a second 2 g dose. A similar tachycardia termination mode was reported by Sager et al[7] in the only 2 patients who responded to magnesium sulfate in their study.

Study limitations: The purpose of the present study was to evaluate the effects of magnesium sulfate on SVT and not the electrophysiologic effects of magnesium sulfate on AV node and accessory pathways in a systematic way. Because of the relatively short-lasting electrophysiologic effects of magnesium observed in our study, we believe that any systematic evaluation of the electrophysiologic effects of magnesium on accessory pathways should be done with high doses of magnesium followed by a maintenance magnesium infusion such that used in the study of DiCarlo et al.[2]

Clinical implications: Intravenous magnesium sulfate was less effective than ATP in terminating induced SVT, and resulted in more marked and prolonged adverse effects at the dosages tested. Because of the vast array of safe and effective drugs available for terminating SVT,[20] there appears to be little role for the clinical use of magnesium sulfate in this setting. However, the observation that magnesium sulfate can directly suppress conduction in accessory pathways, even when these pathways do not exhibit AV node-like properties, is interesting and deserves further study.

Acknowledgment: We are indebted to Anna Harsat and the Department of Clinical Chemistry for performing magnesium serum level determinations.

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An Anatomically Guided Approach to Atrioventricular Node Slow Pathway Ablation

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David Newman, MD, and George Klein, MD

Radiofrequency ablation of the "slow" pathway of the atrioventricular (AV) node reentrant circuit may be guided by electrophysiologic ("slow pathway potential") or anatomic landmarks. Experience with a systematic, anatomically guided approach in 25 patients (20 women and 5 men, aged 38 ± 15 years) with typical AV node reentry is described. The slow pathway is assumed to be the posterior input to the AV node, approaching the nodal region in the corridor between the tricuspid annulus and the orifice of the coronary sinus. A series of radiofrequency lesions are given to interrupt this corridor at its entrance to Koch's triangle. If this is unsuccessful, the series of lesions are repeated progressively at higher levels approaching the AV node. The major end point for success is elimination of the slow pathway as determined by extrastimulus testing. A mean of 1.2 ± 0.2 ablative sessions (20 ± 12 applications of energy) achieved clinical success in 24 of 25 patients (96%) at a follow-up of 8.6 ± 2.2 months. Anterograde Wenckebach cycle length increased from 361 ± 67 ms to 398 ± 70 ms ($p = 0.01$), yet the atrio-Hisian interval in sinus rhythm did not change (69 ± 17 ms before vs 65 ± 15 ms after ablation), $p = 0.22$. Retrograde Wenckebach cycle length was not affected (348 ± 78 ms before vs 366 ± 82 ms after ablation). During ablation, transient third-degree AV block occurred in 6 patients with no permanent sequelae. This approach provides a systematic, expedient technique to eliminate slow pathway conduction based on anatomic landmarks.

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Cure of atrioventricular (AV) node reentry without AV block has been demonstrated using percutaneous techniques and radiofrequency energy.[1–4] Initial enthusiasm for anterior "fast" pathway ablation has been tempered somewhat by a low but unpredictable risk of AV block.[1,4] Recent descriptions of posterior "slow" pathway ablation use electrophysiologic guidance by "slow pathway" potentials[5] or are anatomically guided.[4] We describe our experience with slow pathway ablation using a uniform, systematic application of radiofrequency energy by anatomic guidance.

METHODS

Patients: Twenty-five patients (20 women and 5 men, mean age 38 ± 15 years [range 15 to 70]) undergoing electrophysiologic study and catheter ablation of AV node reentrant tachycardia at the University Hospital, London, Ontario, from March 1991 through January 1992 were included in this study. All had symptomatic AV nodal tachycardia of the anterograde slow and retrograde fast pathway type. No patient had other cardiac disease.

Electrophysiologic studies: Written and verbal informed consent was obtained from all patients. Midazolam was used for sedation and local 2% lidocaine plus systemic alfentanyl were used for pain relief. A baseline electrophysiologic study[6] was performed to confirm the diagnosis of AV node reentry using standard criteria.[7] The study consisted of atrial and ventricular incremental pacing to block and extrastimulus testing using ≥2 drive cycle lengths. All reported refractory periods in this study were performed at a drive cycle length of 600 ms. The stimulation sequence that most clearly demonstrated dual AV node physiology was identified by atrial incremental pacing or extrastimuli from either the high right atrium or proximal coronary sinus. This stimulation sequence served as a quick reference for assessing ablation of the posterior pathway. Four patients did not have dual AV node physiology despite the use of isoproterenol. Elimination of all echo cycles served as the end point for the latter.

Slow pathway ablation procedure: A 7Fr quadripolar steerable 4 mm tip ablation catheter (Mansfield-Webster Catheters, Watertown, Massachusetts) was positioned to identify the His bundle site and then guided into the right ventricle. The left anterior oblique view (60°) confirmed an inferior position at "6 o'clock" on the tricuspid ring (Figure 1). The catheter was then pulled back to the atrial margin of the AV annulus as suggested by a large, sharp ventricular and a much smaller atrial electrogram (position 1 of Figure 2). The right anterior oblique view confirmed the position of the catheter tip near the AV ring. Radiofrequency energy

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was delivered through the distal catheter electrode using a Radionics RFG-3C RF generator system (Radionics, Inc., Burlington, Massachusetts) and a cutaneous patch on the posterior chest. Radiofrequency energy at a current of 500 mA was delivered during sinus rhythm for 40 seconds, while continuously monitoring impedance, voltage, catheter stability and heart rhythm.

Two to 4 subsequent applications of radiofrequency energy were applied in a similar way by incrementally withdrawing the catheter along the 6 o'clock plane guided by direct visualization and by electrogram morphology. The atrial electrogram progressively increased in size relative to the ventricular electrogram as this "pullback" was accomplished (Figure 2). Assessment for dual pathway physiology was performed after each pullback sequence. If slow pathway conduction persisted, the catheter was guided into the right ventricle and the process repeated in a more anterior line in the 5:30 or 5 o'clock plane of the tricuspid ring (Figure 3). Subsequent lines of ablation proceeded anteriorly up to the point at which a His bundle electrogram could be recorded. The baseline electrophysiologic study was repeated ≥30 minutes after loss of the slow pathway.

Follow-up: All patients were followed by telephone and by confirmation with their local medical doctor. A repeat electrophysiologic study was not systematically performed.

Statistical analysis: Values are expressed as mean ± SD. Student's paired, 2-tailed *t* test was used for repeated measurements.

RESULTS

Electrophysiologic results: At baseline study, 22 patients (88%) had inducible reentrant tachycardia with a cycle length of 390 ± 75 ms. The anterograde Wenckebach cycle length of the AV node was 361 ± 67 ms before ablation. Twenty-one patients (84%) had demonstrable dual AV node pathways. Three patients had no retrograde ventriculoatrial conduction and the retrograde Wenckebach cycle length was 348 ± 78 ms in the remaining patients.

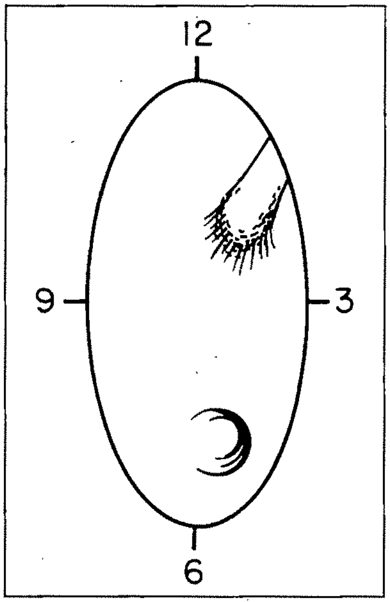

FIGURE 1. Schematic left anterior oblique view from the ventricular aspect of the tricuspid ring. The ring is viewed as an oval clock face with the numbers representing the hours of the clock. The atrioventricular node is seen at approximately 2 o'clock and the coronary sinus ostium at 5 o'clock.

Acute results: Thirty procedures were performed in 25 patients (mean 1.2, range 1 to 2). A single procedure was performed in 20 patients (80%). Clinical recurrence was the indication for a second procedure. The mean number of energy applications (including all sessions) for each patient was 20 ± 12 (range 1 to 43) for a mean duration of 400 seconds (range 30 to 1,174).

Junctional tachycardia occurred during energy application at the successful site in 23 patients (92%) (Figure 4). One patient without junctional tachycardia was successfully ablated with a single energy application during reentrant tachycardia. Twenty-one patients (84%) had successful ablation sites along the 4 to 5 o'clock planes (Figure 1). One patient had success at 3 o'clock and 3 patients at 6 o'clock. The total fluoroscopy time, including the diagnostic study, required for the ablation was 32 ± 14 minutes per session.

Temporary third-degree AV block occurred in 6 patients requiring immediate cessation of energy delivery. The longest duration of high-grade block was 32 seconds. Each episode of third-degree AV block was preceded by junctional tachycardia. No patient required permanent pacing.

The effects of ablation on the AV node's refractory and conduction properties are summarized in Table I. There was no change in the atrio-Hisian interval. Both the anterograde Wenckebach cycle length and the ef-

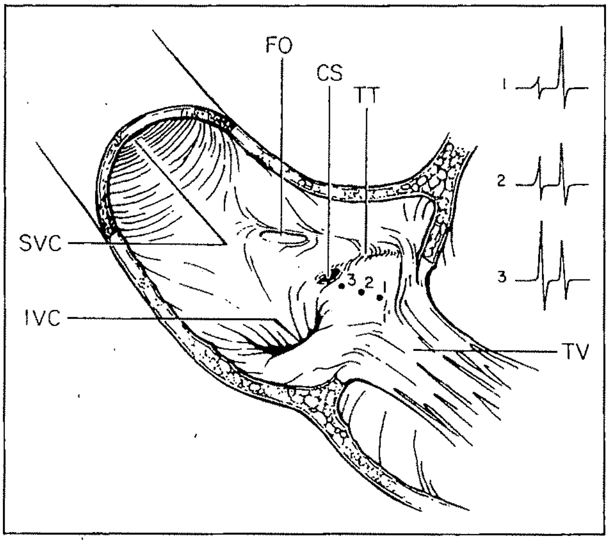

FIGURE 2. Right anterior oblique view of the right atrium and tricuspid ring. Positions 1, 2 and 3 on the atrium represent 3 consecutive sites of ablation during a pullback. These would initially be placed along the 6 o'clock plane of the left anterior oblique view of the tricuspid ring. The corresponding electrograms of positions 1, 2 and 3 demonstrate the increasing size of the atrial electrogram relative to the ventricular electrogram. Following position 3, the catheter would be moved into the right ventricle and pulled back along the 5 o'clock plane of the tricuspid ring once again applying sequential lesions.
CS = coronary sinus ostium; FO = foramen ovale; IVC = inferior vena cava; SVC = superior vena cava; TT = tendon of Todaro; TV = tricuspid valve.

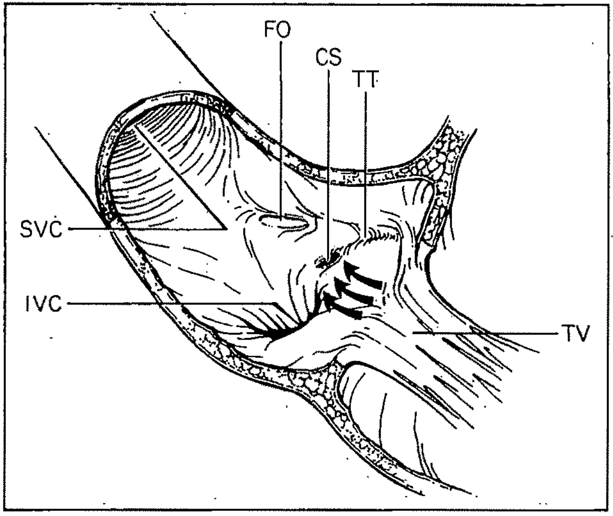

FIGURE 3. Systematic planes of ablation *(3 arrows)* beginning at the inferior margin of the tricuspid valve at the "base" of Koch's triangle and moving toward the apex of the triangle. Each *arrow* corresponds to positions 1, 2 and 3 of Figure 2. Following each "run" of ablation lesions along a single arrow, atrial extrastimulus testing is repeated. If dual pathway physiology persists, ablation lesions are placed along the next superior arrow's plane. In this way a grid-like pattern of ablation lesions is achieved. Abbreviations as in Figure 2.

fective refractory period were increased by ablation. This was due to loss of slow pathway conduction. The retrograde Wenckebach cycle length was not altered, yet the effective refractory period was increased (p = 0.01). These data exclude the 3 patients who had no retrograde AV conduction before ablation and the additional 2 who had none after ablation.

Follow-up results: Patients were followed up for a mean of 8.6 ± 2.2 months. One patient has had recur-

TABLE I Electrophysiologic Results of Ablation

	Before Ablation	After Ablation	No. of Pts.	p Value
Anterograde				
AH interval	69 ± 17	65 ± 15	25	0.22
ERP FP	350 ± 55	305 ± 60	21	0.08
ERP SP	270 ± 45	—	21	—
WCL	361 ± 67	398 ± 70	25	0.01
Retrograde				
ERP	255 ± 50	325 ± 100	19	0.01
WCL	348 ± 78	366 ± 82	20	0.10
No VA cond.	3	5		

All values are in milliseconds ± SD. p values are paired, 2-tailed Student's *t* test.
AH = atrio-Hisian interval; ERP FP = fast pathway effective refractory period at 600 ms; ERP SP = slow pathway effective refractory period at 600 ms; VA cond. = ventriculoatrial conduction; WCL = Wenckebach cycle length.

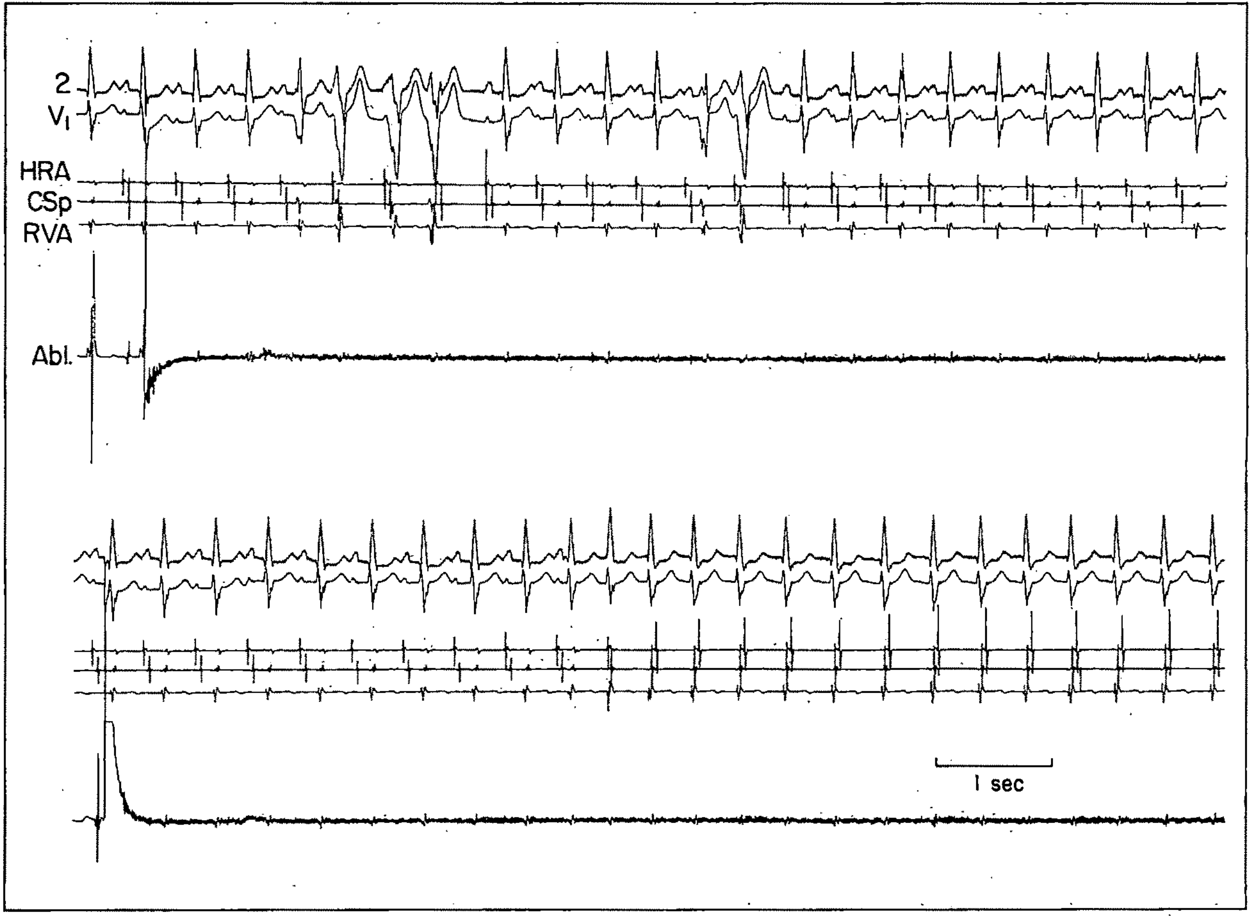

FIGURE 4. Radiofrequency ablation at base of Koch's triangle. The initial site *(top panel)* corresponds to site 1 in Figure 2. Onset of current after the first cycle results in ventricular ectopic activity, suggesting that the ablation tip is positioned too distally. A slight pullback *(bottom panel)* results in junctional tachycardia after which the slow pathway was lost. Abl. = ablation catheter; CSp = proximal coronary sinus; HRA = high right atrial electrogram; RVA = right ventricular apex.

rence of tachycardia with minimal symptoms requiring no further therapy. This yields a success rate of 96% (24 of 25 patients).

DISCUSSION

The feasibility of altering the AV node to cure AV node reentrant tachycardia was suggested in 1979 when an attempt at surgical ablation of the AV node resulted in AV node reentrant tachycardia cure without complete AV block.[8] Similarly, a registry of catheter His bundle ablation using direct-current shocks reported a subgroup of patients with AV node reentrant tachycardia who failed ablation yet remained cured of tachycardia.[9] Subsequently, several operative techniques were described using perinodal dissection or cryosurgery, which were very effective in eliminating AV node reentry and preserving normal AV conduction.[10-15] This cumulative data clearly suggested that part of the AV node reentrant tachycardia circuit was extranodal or at least not necessary for normal AV nodal conduction. This provided the rationale for subsequent attempts at eliminating this part of the circuit by catheter ablation. Initial ablative attempts using direct-current energy met with limited success and unpredictable block.[3] These directed energy to the retrograde limb of the circuit or titrated energy to create subtotal injury rendering the node incapable of reentry.[3] Radiofrequency energy allowed more discrete lesions and initially was directed at sites inferior and posterior to the recorded His bundle electrogram in an attempt to injure the fast pathway.[1]

Hazlitt et al[5] recently suggested that the slow pathway is a distinct anatomic entity and that slow potentials can be identified to guide their ablation. Others have shown that the slow pathway can be ablated by anatomically guided radiofrequency energy application in the region of the coronary sinus ostium without recording discrete potentials.[4] The data in this report further support the view that the slow pathway is extranodal or at least peripheral to the compact node and can be ablated with minimal risk of AV block. Neither anterograde nor retrograde "fast pathway" conduction is affected. The slow pathway may well be the posterior or crista terminalis input into the AV node[14] and its location near the "base" of Koch's triangle is probably relatively constant. The technique described ablates the area of interest in a grid-like, systematic fashion moving from the base toward the "apex" of Koch's triangle and can be replicated reasonably from patient to patient. Success is usually heralded by junctional tachycardia.[16] At early follow-up, only 1 patient has had recurrence of tachycardia after the ablation procedures and no patient has developed permanent high-degree AV block, attesting to the efficacy and safety of the procedure.

Study limitations: The technique described potentially involves ablating a larger area than might be necessary if the procedure were guided by a specific slow pathway potential. This may be a reasonable trade-off for a technically simpler and perhaps shorter procedure with less radiation exposure. Further clinical follow-up is required to assess long-term efficacy and potential adverse effects of this procedure including late AV block or arrhythmogenesis.

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Renal Response to Indomethacin in Congestive Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

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The impact of nonsteroidal anti-inflammatory drugs (NSAIDs) on renal function has not been evaluated in patients with congestive heart failure. Therefore, the renal effects of indomethacin were examined in patients with chronic heart failure, and the relation between the changes in glomerular filtration rate and renal plasma flow after indomethacin administration was assessed. Twenty-five patients with congestive heart failure and an ejection fraction <40% were evaluated. At baseline, renal plasma flow and glomerular filtration rate were measured, using disappearance from the serum of intravenously injected ^{131}I-orthodihippurate and urinary accumulation of intravenously injected technetium-99m diethylenetriamine pentaacetic acid, respectively. After 3 days, 75 mg of sustained release indomethacin were administered, and repeat renal function tests were performed. Mean glomerular filtration rate decreased from 40 ± 21 to 32 ± 16 ml/min/1.73 m^2 ($p < 0.05$), and mean renal plasma flow decreased from 242 ± 122 to 222 ± 110 ml/min/1.73 m^2 ($p < 0.05$). There was no correlation between the changes in glomerular filtration rate and renal plasma flow after indomethacin administration. It is concluded that 1 dose of an NSAID may cause marked and clinically important alterations in renal function in patients with heart failure. However, the decrease in glomerular filtration rate does not merely reflect a decrease in renal plasma flow, but probably the effects of NSAIDs on the intraglomerular actions of prostaglandins.

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Nonsteroidal anti-inflammatory drug (NSAID)-induced vasoconstriction leads to decreased cardiac output and increased ventricular filling pressures in patients with heart failure,[1] but these actions are frequently seen as clinically irrelevant. The possible adverse renal consequences of NSAIDs are similarly ignored. Vasoconstriction of systemic arteries and renal arterioles can decrease renal plasma flow, and activation of intracellular contractile components within mesangial cells may decrease the glomerular capillary surface filtering area. NSAIDs decrease glomerular filtration rate and renal plasma flow in subjects with dehydration[2] or cirrhosis,[3] persons with neurohormonal activation similar to that observed in patients with heart failure. NSAIDs also impair both renal plasma flow and glomerular filtration rate in dogs with reduced cardiac output.[4] Despite the concerns regarding NSAID-induced reductions in glomerular filtration rate, the renal effects of NSAIDs have not been studied in patients with heart failure. Therefore, we investigated the impact of NSAIDs on renal function, specifically examining whether changes in glomerular filtration rate are secondary to those in renal plasma flow or to the intrinsic glomerular actions of indomethacin.

METHODS

Patients: We studied 25 patients (18 men and 7 women, aged 26 to 74 years, mean 59 ± 14) with severe left ventricular dysfunction and a serum creatinine concentration <3.5 mg/dl. All patients had a left ventricular ejection fraction <40% by radionuclide angiography (range 9 to 38%, mean 22 ± 8%). Mean plasma renin activity was markedly increased (3.6 ± 3.8 ng/ml/hour) and confirmed the severity of disease. The cause of heart failure was ischemic heart disease in 8 patients and dilated cardiomyopathy in 17. Nineteen patients were classified as New York Heart Association functional class III, and 6 as class IV, but all were clinically stable and receiving constant doses of digoxin and diuretics. Most patients had not been treated with angiotensin-converting enzyme inhibitors, which were discontinued ≥30 days before entry in the study in any patient who had received these agents for >1 week. Before renal evaluation, patients received no vasodilator drugs for ≥5 days and no NSAID (including aspirin) for ≥14 days. All diuretic and cardioactive medications were withheld on the morning of renal hemodynamic measurements.

Study protocol: After written informed consent was obtained and clinical stability was established, baseline determinations of renal hemodynamics were obtained,

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as outlined later. After 3 days, 75 mg of sustained-release indomethacin (Indocin SR®) were administered 30 minutes before injection of technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc DTPA) and ^{131}I-orthodihippurate. Renal hemodynamic determinations were then repeated. The protocol was approved by the human volunteers research committee of the University of Maryland.

Measurements of renal hemodynamics: Renal plasma flow was measured by assessing the disappearance from the serum of 60 μCi of ^{131}I-orthodihippurate at precisely 44 minutes after injection, as described by Tauxe et al.[5] Glomerular filtration rate was determined by the urinary accumulation of ^{99m}Tc DTPA, as described by LaFrance et al.[6] Urine was collected hourly between 1 and 4 hours after injection of 200 μCi of ^{99m}Tc DTPA, and serum samples were obtained 1, 2, 3 and 4 hours after injection. Three 1-hour measurements of glomerular filtration rate were computed, corrected for body surface area and averaged. If any 1-hour urine sample was not obtained, glomerular filtration rate was determined from the combined urinary accumulation between 1 and 4 hours. Because renal plasma flow was determined 0 to 44 minutes after isotope injection, glomerular filtration rate was also assessed from 60 to 120 minutes after injection to more contemporaneously compare the 2 parameters.

Data analysis: The renal hemodynamic response to indomethacin was evaluated by comparing the renal function determinations at baseline with those after indomethacin administration, using a 2-tailed *t* test for paired data. Comparison of the change in renal plasma flow and the change in glomerular filtration rate was performed using linear regression analysis. Group data are expressed as mean ± SD.

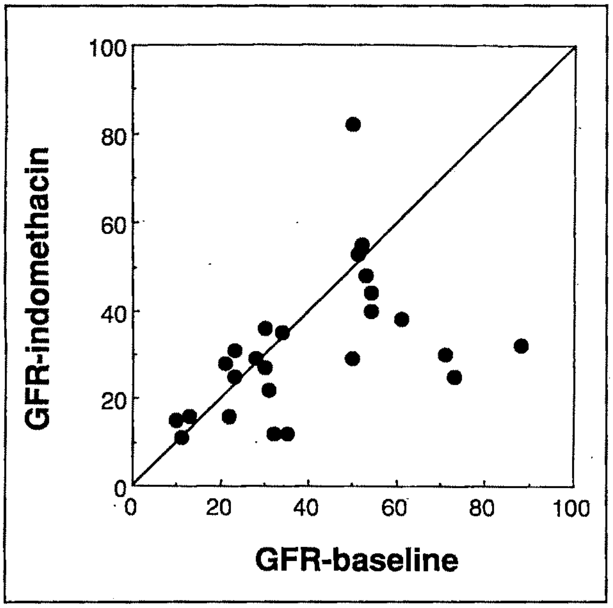

FIGURE 1. Glomerular filtration rate (GFR) before and after administration of sustained release indomethacin in each of 25 patients. Line of identity is drawn. Mean GFR decreased from 40 ± 21 to 32 ± 16 ml/min/1.73 m^2 ($p < 0.05$). GFR decreased by >10 ml/min/1.73 m^2 in 9 patients, but only 1 had a similar increase.

RESULTS

Renal hemodynamic response to therapy: Mean glomerular filtration rate decreased from 40 ± 21 to 32 ± 16 ml/min/1.73 m^2 ($p < 0.05$) after 1 dose of indomethacin; 9 of 25 patients (33%) had a reduction ≥10 ml/min/1.73 m^2 (Figure 1). Mean renal plasma flow decreased from 242 ± 122 to 222 ± 110 ml/min/1.73 m^2 ($p < 0.05$); 15 patients (60%) had a reduction ≥10 ml/min/1.73 m^2 (Figure 2).

Comparison of changes in renal plasma flow and glomerular filtration rate: To determine the relation between the changes in glomerular filtration rate and renal plasma flow, we compared the changes in these 2

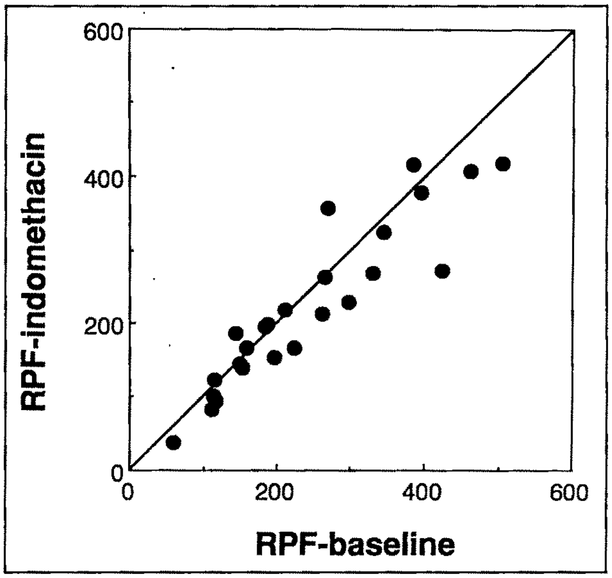

FIGURE 2. Renal plasma flow (RPF) before and after administration of sustained-release indomethacin in each of 25 patients. Line of identity is drawn. Mean RPF decreased from 242 ± 122 to 222 ± 110 ml/min/1.73 m^2 ($p < 0.05$).

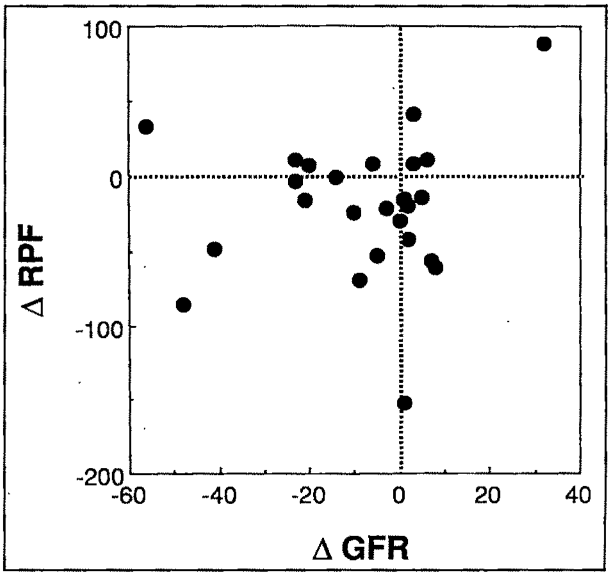

FIGURE 3. Change in glomerular filtration rate (Δ GFR; ml/min/1.73 m^2) after indomethacin compared with that in renal plasma flow (Δ RPF; ml/min/1.73 m^2). There was no relation between these 2 parameters. Marked changes in 1 parameter were not necessarily accompanied by changes in the other.

parameters for each patient. There was no correlation between the changes in glomerular filtration rate and renal plasma flow after indomethacin administration (Figure 3). Marked reductions in glomerular filtration rate were occasionally associated with decreases in renal plasma flow, but were just as often associated with increased renal plasma flow. Similarly, a decrease in renal plasma flow was not necessarily accompanied by a reduction in glomerular filtration rate.

To ensure that the absence of relation between glomerular filtration rate and renal plasma flow was not secondary to the different times at which they were determined, we performed an additional calculation of glomerular filtration rate as close as possible to the time during which renal plasma flow was assessed. Because renal plasma flow was determined 0 to 44 minutes after isotope injection, we assessed glomerular filtration rate between 60 and 120 minutes after isotope administration. Mean glomerular filtration rate calculated during this time decreased from 43 ± 26 to 32 ± 15 ml/min/1.73 m^2, and there was no relation between glomerular filtration rate and renal plasma flow.

Effect of indomethacin on blood pressure: Blood pressure did not change with indomethacin administration. Mean arterial pressure was 99 ± 12 mm Hg at baseline and 99 ± 13 mm Hg after indomethacin. There was no correlation between the changes in renal function and mean arterial pressure.

DISCUSSION

One dose of indomethacin caused a marked decrease in glomerular filtration rate in one third of severely ill patients with congestive heart failure who were studied as part of this investigation. Although mean renal plasma flow also decreased in these patients, the decrease in glomerular filtration rate was not due to alterations in renal plasma flow; there was no association between the changes in glomerular filtration rate and renal plasma flow.

Glomerular filtration rate: The present study is the first to evaluate the renal effects of an NSAID in patients with congestive heart failure. The marked decrease in glomerular filtration rate detected after only 1 dose of indomethacin suggests that use of these agents may have important clinical consequences in patients with heart failure. The findings are consistent with those in previous evaluations of the effects of NSAIDs in patients with other conditions that lead to stimulation of multiple neurohormonal systems. NSAIDs do not alter glomerular filtration rate in normal subjects,[7] but changes in glomerular filtration rate have been consistently found in patients with dehydration[2] or cirrhosis.[3]

Neurohormonal activation has important renal consequences. Whereas increased concentrations of angiotensin II may help to preserve renal function by maintaining arterial and glomerular capillary pressure, other actions can lead to impaired glomerular filtration. For example, the vasoconstriction that maintains arterial pressure may decrease nephron plasma flow.[8] Activation of the intracellular contractile components within mesangial cells can lead to a decease in the filtering surface area and glomerular filtration.[9] Intrarenal angiotensin II has been found to decrease glomerular ultrafiltration in patients with sodium depletion[10] and congestive heart failure.[11]

Prostaglandins may be particularly important for maintenance of renal function in patients with activation of the renin-angiotensin and arginine vasopressin systems. Prostaglandins counteract many of the adverse renal actions of angiotensin II. First, they act to increase the renal plasma flow.[12] Second, prostaglandin E_2 decreases the contractile response of glomeruli to angiotensin II, limiting the angiotensin II–induced decrease in surface area.[13] Similarly, prostaglandin synthesis may permit the renal vasculature to be spared from the generalized vasoconstriction due to arginine vasopressin.[14] Therefore, it is not surprising that the effects of prostaglandins are most evident in the presence of angiotensin II and vasopressin.[15] The interdependence of these systems is further emphasized by the finding that angiotensin II and vasopressin may directly lead to prostaglandin production.[16] The NSAID-induced deterioration in renal function that we observed supports the concept that prostaglandins are essential to counter the renal deleterious effects of neurohormonal activation.

Relation of glomerular filtration rate and renal plasma flow: A reduction in renal plasma flow can decrease glomerular filtration rate.[17] Previous reports of a correlation between glomerular filtration rate and renal plasma flow in patients with heart failure further suggested a causal relation between the 2 parameters.[18] However, in the present study, indomethacin caused only a small reduction in mean renal plasma flow, and more importantly, there was no relation between the direction and magnitude of the changes in renal plasma flow and glomerular filtration rate. Other studies also found relatively small decreases in renal plasma flow compared with those in glomerular filtration rate after administration of an NSAID.[2] These findings argue against the hypothesis that decreased renal plasma flow is the mechanism by which NSAIDs decrease glomerular filtration rate. It is more likely that the intraglomerular actions of prostaglandins are the important determinants of their effects on glomerular filtration.

Study limitations: This study should be interpreted with regard to a few limitations. First, we evaluated the effects of 1 dose of indomethacin. It is possible that the acute deleterious actions of indomethacin may be mitigated by its chronic administration. A previous study reported that glomerular filtration rate and renal plasma flow decreased acutely in patients with renal insufficiency receiving NSAIDs, but returned to baseline after 5 days of chronic administration.[19] We believe it unlikely that patients with heart failure would have a similar return to baseline renal function. The renal hemodynamic abnormalities of patients with neurohormonal activation are probably more severe and prolonged than those with renal insufficiency who have no effects from the chronic use of NSAID. Unlike the latter patients, patients with heart failure-induced, marked, neurohormonal activation do not have the capability of counter-ing impaired prostaglandin production with adjustment of other homeostatic systems.

This study is also limited by the technical inability to measure glomerular filtration rate and renal plasma flow at exactly the same time. The glomerular filtration rate was assessed from 60 to 240 minutes after isotope injection, whereas renal plasma flow was assessed 0 to 44 minutes after the injection. Therefore, it is possible that the absence of correlation between renal plasma flow and glomerular filtration rate may be a temporal discrepancy in the assessment of the 2 parameters. However, a number of factors argue against such a conclusion. First, the pharmacokinetics of Indocin SR suggest that peak plasma levels should be achieved by 30 minutes after drug administration (time 0 after isotope injection) and remain constant for hours.[20] Second, analysis of glomerular filtration rate determined as near as possible (between 60 and 120 minutes after indomethacin administration) to assessment of renal plasma flow confirmed the absence of any correlation between the 2 parameters.

It should be appreciated that the sodium balance of a patient may affect renal function, and this factor was not strictly regulated in the present study. Varying sodium intake and the use of diuretics will impact on renal prostaglandin synthesis[21] and could interfere with renal function determinations. However, the absence of precise sodium balance control should not alter the conclusions of this study. All patients served as their own controls, were on the same diet, at stable weight and in the same clinical condition during both evaluations. Diuretics were withheld the morning of each study, and medications had been stable for ≥5 days.

The findings are consistent with most previous studies of the renal effects of various NSAIDs in patients with neurohormonal activation.[22] However, the present study was performed with 1 NSAID (indomethacin) and may not be applicable to all such agents. For example, sulindac does not decrease urinary prostaglandin concentrations in normal subjects to the same extent as does indomethacin.[23] Sulindac has not been evaluated in patients with heart failure, and the clinical implications of its particular renal actions remain unknown. Until studies demonstrate the safety of a particular agent, all NSAIDs should be considered potentially dangerous in patients with congestive heart failure.

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Clinical Characteristics of Patients in Studies of Left Ventricular Dysfunction (SOLVD)

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The Studies of Left Ventricular Dysfunction (SOLVD) trials were designed to evaluate the effects of enalapril on long-term mortality in patients with severe left ventricular (LV) dysfunction. Patients with LV ejection fractions ≤0.35 and symptoms of congestive heart failure (CHF) were enrolled in the treatment trial, whereas those with no history of overt CHF and taking no treatment directed for LV dysfunction were enrolled in the prevention trial. The baseline clinical characteristics of SOLVD patients were compared to characterize differences between patients in these 2 separate but concurrent trials. From over 70,000 patients screened with LV dysfunction, 4,228 patients were enrolled in the prevention trial and 2,569 patients in the treatment trial. Ischemic heart disease was the primary cause of LV dysfunction in both prevention (83%) and treatment (71%) trial patients. Prior myocardial infarction was present in 80% of the prevention and 66% of the treatment trial patients ($p < 0.001$). In the prevention trial, infarction was recent (≤6 months) in 27% patients and remote (>6 months) in 57% patients. Treatment trial patients had proportionately more women (20 vs 13%; $p < 0.001$) and non-Caucasians (20 vs 14%; $p < 0.001$), as well as the coexisting risk factors of hypertension (42 vs 37%; $p < 0.001$) and diabetes (26 vs 15%; $p < 0.001$) than did prevention trial patients. Treatment trial patients were more likely to have the clinical signs associated with CHF and had a lower mean LV ejection fraction (0.25 ± 0.07 vs 0.28 ± 0.06, $p < 0.001$) than prevention trial patients. Clinical characteristics of patients in both trials were influenced by the gender and race of enrolled patients. Similarly, coronary artery bypass surgery was performed less often in women and non-Caucasians. Thus, the baseline database of patients enrolled in the SOLVD trials demonstrates the varied clinical features associated with severe LV dysfunction and highlights the impact of symptomatic status, gender and race on clinical presentation.

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Despite a favorable trend in mortality of a broad range of cardiovascular diseases, congestive heart failure (CHF) has emerged as a unique problem. The number of deaths either solely or in part due to CHF has risen dramatically over the past 3 decades.[1] Despite improved diagnostic techniques and more drugs, mortality due to CHF remains high, and has been estimated to be at a rate of 4 to 8 times that of the general population of the same age.[2] Moreover, patients with CHF frequently have coexisting diseases,[3,4] further contributing to the multiplicity of problems that patients with this syndrome encounter. Progress in combatting CHF has centered around our ability to identify patients at greater risk for subsequent events and the development of newer therapeutic agents that potentially modify risk, or at a minimum, prevent worsening CHF. These concepts have been further extended in the conduct of clinical trials designed to assess efficacy of newer therapeutic agents in specific subgroups of patients with CHF. Examples include trials evaluating the usefulness of angiotensin-converting enzyme inhibitors in patients ranging from those with mild-moderate[5] to severe CHF.[6]

The Studies of Left Ventricular Dysfunction (SOLVD) trial were initiated in 1986 to evaluate the effects of enalapril on long-term mortality and major morbidity in the broad spectrum of patients with left ventricular (LV) dysfunction. By design, SOLVD encompassed 2 concurrent but separate trials: a prevention trial, which enrolled patients with a low ejection fraction and no overt CHF; and a treatment trial, which enrolled patients with a low ejection fraction and symptoms and signs of CHF.

The database of baseline characteristics of patients in SOLVD provides several unique opportunities. First, it is the largest sample ever compiled of patients with LV dysfunction, involving nearly 7,000 patients from 3 different countries. Second, inclusion/exclusion criteria were liberalized so that a broad representation of patients with LV dysfunction were enrolled. The resultant

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enrollment consists of patients with multiple etiologies, receiving numerous medications, and encompassing the range and types of patients normally encountered in everyday clinical practice, thus providing a basis for widespread generalizability of the trial's findings. The aims of this study were to (1) characterize the differences between patients with severe LV dysfunction and symptoms of CHF (treatment trial) and those with no history of overt CHF and not receiving therapy for CHF (prevention trial), and (2) highlight differences in presentation by gender and race.

METHODS

Recruitment: The planning phase of the SOLVD program was initiated in 1984. Patient enrollment began in July of 1986. Recruitment was performed at 23 clinical centers (United States, 20; Canada, 2; Belgium, 1). A total of 93 hospitals participated. A detailed list of participating institutions, investigators and study coordinators has been previously published.[7] Screening logs were maintained at 23 centers identifying patients with LV ejection fractions ≤0.40. Patients who had an ejection fraction ≤0.35 were enrolled in either the treatment or prevention trial on the basis of symptoms of CHF or need for therapy for CHF symptoms, or both. Exclusion criteria, published elsewhere,[7] fall into several broad categories: noncardiac diseases likely to limit long-term survival, such as cancer and other significant systemic illnesses; hemodynamically significant valvular outflow tract obstruction; congenital heart disease; pericardial disease; or unstable ischemic coronary syndromes. Recent myocardial infarction, coronary artery bypass surgery or angioplasty were temporary exclusions because the patient could be enrolled 30 days later.

Classification into prevention versus treatment trial: Before enrollment, SOLVD investigators reviewed each patient for the presence or absence of clinical symptoms or signs of overt CHF. Patients who met these previously mentioned eligibility criteria and who had little or no limitation of exercise tolerance due to dyspnea or fatigue, and did not require treatment with digitalis, diuretics or vasodilators for heart failure were considered eligible for the prevention trial. Therefore, prevention trial patients can be viewed as belonging to 1 of the following 2 groups: patients with LV ejection fraction ≤0.35 who were not taking any cardiac medication, or those with LV ejection fraction ≤0.35 who required medication for cardiovascular problems other than heart failure. This latter group includes patients taking β blockers, calcium antagonists or nitrates for angina, diuretics for coexisting systemic hypertension or edema due to significant peripheral venous insufficiency, or digoxin for supraventricular arrhythmias. Participants with overt heart failure with shortness of breath on exertion, evidence of fluid retention, pulmonary congestion, and who required treatment with diuretics, inotropic drugs, or vasodilators, or a combination of these, for symptomatic relief were eligible for the treatment trial.

Baseline clinical variables: Standard clinical variables documented during the randomization visit are presented in this report. They can be broadly classified under the general headings of physical characteristics, demographics, history of coexisting diseases, symptomatic status, current medications, history of presence or absence of prior myocardial infarction, whether or not cardiac surgery or other cardiac procedures were performed, and laboratory data (chest x-ray, electrocardiogram, ejection fraction, as well as clinical chemistry). LV ejection fraction was measured with radionuclide angiography (68% of patients), contrast angiography (11%) or 2-dimensional echocardiography (21%) with the area-length method or modified Simpson's Rule.[8,9] The protocol was approved by the institutional review board of each center. Patients provided written consent before their entry into the study.

Statistical methods: Differences in baseline characteristics between the 2 patient groups were evaluated by the Mantel-Haenszel chi-square tests with Bonferroni adjustment for multiple comparisons. For continuous data, 1-way analysis of variance comparisons were obtained. Group data are represented as mean ± standard deviation. A p value <0.05 after Bonferroni correction was considered significant.

RESULTS

Prerandomization phase: A summary of recruitment of eligible patients is outlined in Figure 1. Age and ejection fraction eligibility criteria were met by 55,069 patients; however, of these, 47,581 patients were either ineligible or refused to participate. The remaining 7,488 patients were enrolled in a run-in period with test dosing and a stabilization phase, which resulted in a further 691 patients excluded. Reasons for either preenrollment or prerandomization exclusion have been previously reported.[10] The 6,797 patients entered into the study represented 12% of patients with an LV ejection fraction ≤0.35 identified at participating centers.

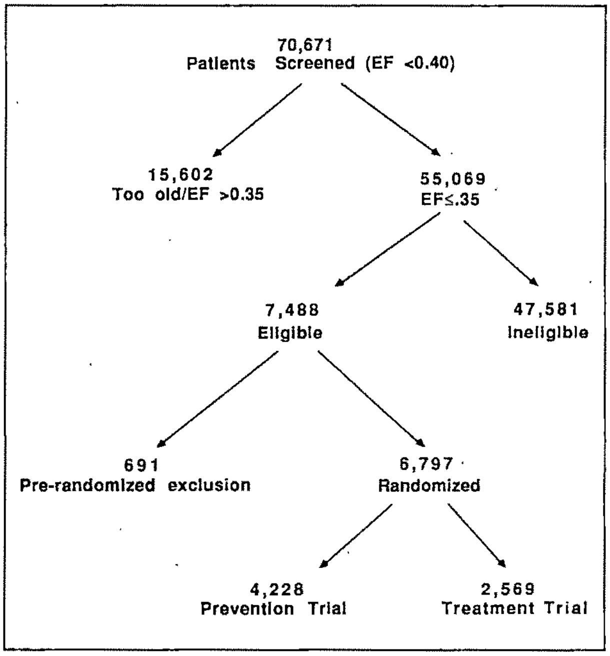

FIGURE 1. Recruitment summary for patients in the SOLVD trial. EF = ejection fraction.

TABLE I Percentage of Discrete Baseline Variables in SOLVD Patients*

Variable	Prevention	Treatment	Chi-Square p Value†
Men/women	87/13	80/20	<0.001
Non-Caucasian	14	20	<0.001
History of			
Systemic hypertension	37	42	<0.001
Diabetes mellitus	15	26	<0.001
Chronic lung disease	5	10	<0.001
Cerebrovascular disease	6	8	NS
Myocardial infarction	80	66	<0.001
Coronary bypass/angioplasty	37	29	<0.001
Symptoms of			
Angina	34	38	NS
Dizziness	15	21	<0.001
Orthopnea	6	43	<0.001
Edema	10	46	<0.001
New York Heart Association class			
I	67	11	<0.001
II	33	57	<0.001
III	—	30	<0.001
IV	—	2	<0.001
Physical exam			
Atrial fibrillation	4	10	<0.001
Rales	2	12	<0.001
Edema	4	17	<0.001
Elevated jugular venous pressure	2	11	<0.001
S_3	5	24	<0.001
Chest x-ray			
Cardiothoracic ratio >0.5	40	57	<0.001
Pulmonary venous congestion	6	23	<0.001
Electrocardiogram			
Q-wave myocardial infarction	63	45	<0.001
Location			
Anterior	34	23	NS
Inferior	20	15	NS
Both	7	4	NS
LV hypertrophy	13	23	<0.001
LV ejection fraction			
<15	2	7	<0.001
15–19	6	16	<0.001
20–24	15	21	<0.001
25–29	26	24	<0.001
30–35	51	31	<0.001
Primary cause of CHF			
Ischemic	83	71	<0.001
Other	7	10	<0.001
Unknown	9	18	<0.001

*Percentages are based on the 4,215 prevention and 2,568 treatment trial participants for whom baseline data are available.
†p <0.001 after a Bonferroni adjustment for multiple comparisons.
CHF = congestive heart failure; LV = left ventricular; NS = not significant; SOLVD = Studies of Left Ventricular Dysfunction trial.

TABLE II Baseline Clinical and Laboratory Variables Grouped According to Trial Assignment

Variable	Prevention (n = 4,215)	Treatment (n = 2,568)	ANOVA p Value
Age (year)	59 ± 10	61 ± 10	<0.001
Weight (lb)	180 ± 33	177 ± 38	<0.001
Blood pressure (mm Hg)			
Systolic	125 ± 17	125 ± 18	NS
Diastolic	78 ± 10	77 ± 10	<0.01
Heart rate (beats/min)	75 ± 13	80 ± 13	<0.001
Cardiothoracic ratio	0.50 ± 0.06	0.53 ± 0.07	<0.001
LV ejection fraction	0.28 ± 0.06	0.25 ± 0.07	<0.001
Blood tests			
Sodium (mEq/liter)	140.2 ± 3	139.6 ± 3	<0.001
Potassium (mEq/liter)	4.3 ± 0.3	4.3 ± 0.5	<0.001
Blood urea nitrogen	17 ± 6	20 ± 8	<0.001
Creatinine (mg/dl)	1.1 ± 0.3	1.2 ± 0.3	<0.001

ANOVA = analysis of variance; LV = left ventricular; NS = not significant.

TABLE III Percent Distribution of Concomitant Medications

Medication	Prevention (n = 4,215)	Treatment (n = 2,568)	Chi-Square p Value*
Digitalis	13	67	<0.001
Diuretic	18	85	<0.001
Thiazide	9	11	NS
Loop	7	75	<0.001
Metalazone	00.1	2	<0.001
Potassium sparing	4	9	<0.001
Potassium supplement	6	50	<0.001
Antiarrhythmic	15	22	<0.001
β blocker	23	8	<0.001
Calcium antagonist	35	31	<0.001
Antiplatelet	51	33	<0.001
Nitrates	30	42	<0.001
Anticoagulant	12	16	<0.001

*p <0.001 after a Bonferroni adjustment for multiple comparisons.
NS = not significant.

Prevention versus treatment trial patients: The baseline characteristics of patients in either trial are summarized in Tables I to III. Patients in the prevention trial were younger and had fewer women and non-Caucasians than treatment trial patients. Prevention trial patients had lower heart rates; however, systolic and diastolic blood pressure was comparable in both groups. Patients in the prevention trial were less likely to have a history of concomitant systemic hypertension, diabetes mellitus and chronic lung disease than patients in the treatment trial. More prevention trial patients had a history of myocardial infarction and revascularization procedures (bypass surgery/coronary angioplasty). Based on the preestablished eligibility criteria for the individual trials, treatment trial patients more frequently had symptoms and clinical findings normally associated with heart failure. The majority of prevention trial patients were in New York Heart Association class I, whereas most of the treatment trial patients were either in class II or III, with only 2% of patients being in class IV. Atrial fibrillation was present twice as often in the treatment trial patients than in the prevention trial patients.

The 2 patient subgroups differed markedly in their current use of medications. The majority of treatment trial patients were receiving other therapy for heart failure. Sixty-seven percent of treatment trial patients were taking digoxin, 85% were taking a diuretic drug and only 6.5% were taking neither digoxin nor a diuretic. In the prevention trial, 13% of patients were taking digoxin for supraventricular rhythm disturbances, and 18% were taking diuretics for either hypertension or limb swelling due to venous disease. Most of the prevention trial patients (73%) were taking neither digitalis nor a diuretic. More prevention trial patients were taking β-blocker therapy, whereas approximately one-third

TABLE IV Baseline Characteristics and Drug Therapy of Patients in the Prevention Trial Based on Presence or Absence of Recent Myocardial Infarction

Characteristic	MI ≤6 Months (n = 1,139)	No MI or MI >6 Months (n = 3,088)
	Mean ± SD	
Age (year)	58 ± 11	60 ± 10*
Blood pressure (mm Hg)		
Systolic	121 ± 16	127 ± 16*
Diastolic	77 ± 9	78 ± 10*
Heart rate	74 ± 12	75 ± 12
Cardiothoracic ratio	0.50 ± 0.06	0.50 ± 0.06
LV ejection fraction	0.29 ± 0.05	0.28 ± 0.06*
	Percentages†	
Men/women	87/13	89/11
Non-Caucasian	10	14*
History of		
Systemic hypertension	35	38
Diabetes mellitus	16	15
Coronary artery bypass surgery/ percutaneous transluminal coronary angioplasty	37	37
Current angina	38	32*
Physical examination		
Atrial fibrillation	2	5*
Rales	2	2
Edema	4	5
S_3	5	5
Chest x-ray		
Cardiothoracic ratio >0.5	44	39*
Pulmonary venous congestion	9	6*
Primary cause of LV dysfunction		
Ischemic	96	78*
Other	1	9*
Unknown	2	12*
Medication		
Digitalis	10	13*
Diuretic	10	19*
β blocker	32	21*
Calcium antagonist	40	33*
Nitrates	37	30*
Antiplatelet	65	50*
Anticoagulant	17	10*
Antiarrhythmic	14	15

*p <0.001.
†Percentages are based on 4,227 prevention trial patients for whom baseline data/myocardial infarction relations are known.
LV = left ventricular; MI = myocardial infarction.

of the patients in both groups were receiving calcium antagonist therapy. Treatment trial patients were more likely to be taking anticoagulation therapy and antiarrhythmic therapy. The mean number of concurrent cardiovascular medications per treatment trial patient was 3.49 ± 1.25 versus 1.95 ± 1.11 in the prevention trial patients.

A higher proportion of patients in the treatment trial had a cardiothoracic ratio >0.5 on chest x-ray than patients in the prevention trial. Fewer patients in both groups had evidence of pulmonary venous congestion; however, this finding was present in more treatment trial patients. Electrocardiographic evidence of Q-wave infarction was present in 63% of prevention trial and only 45% of treatment trial patients (p <0.001). However, the location of the Q-wave infarction was similar in the 2 groups of patients. Several versions of forms were used to determine LV hypertrophy throughout the study, ranging from simply stating whether LV hypertrophy was present (n = 962) to specific guidelines (R-wave voltage in any lead ≥2.6 mV or as peak-to-peak QRS voltage ≥2 mV in any lead) for the presence or absence of LV hypertrophy (n = 3,018). With the former method, electrocardiographic criteria for LV hypertrophy was present in 11% of prevention trial and 22% of treatment trial patients. When specific guidelines were given, LV hypertrophy was present in 14% of prevention trial and 24% of treatment trial patients. Combined data from both methods revealed LV hypertrophy to be more frequently present in treatment trial patients. The ejection fraction of half of the prevention trial patients was in the range of 0.30 to 0.35, whereas less than 3% had LV ejection fractions <0.15. In contrast, only 31% of treatment trial patients had LV ejection fractions of 0.30 to 0.35, and in 7%, the ejection fraction was <0.15.

The primary cause of LV dysfunction in both trials was underlying ischemic heart disease, and was present in 83% of patients in the prevention trial and in 71% of patients in the treatment trial (p <0.001). The cause of LV dysfunction was unknown in 9% of prevention trial and in 18% of treatment trial patients. Less than 10% of either patient subgroup had LV dysfunction secondary to other known specific disease entities.

Patients in the prevention trial were further classified into those with recent (≤6 months) myocardial infarction (n = 1,139) and those with either no history of infarction or with a remote myocardial infarction (>6 months) (n = 3,088), and the results are summarized in Table IV. Those in the group with recent myocardial infarction were slightly younger and had fewer non-Caucasians; however, both groups had a similar proportion of men and women, as well as coexisting risk factors of systemic hypertension and diabetes mellitus. There were only minor differences in the physical and laboratory findings between groups. Mean LV ejection fraction was slightly higher in the group with recent infarction. Ischemic heart disease was the most common underlying cause of LV dysfunction in both groups of patients. Although differences in medication use were documented, considerable overlap existed, perhaps reflecting the prevalence of ischemic heart disease in the 2 patient groups. The number of patients having revascularization procedures was identical in the 2 groups of patients.

Gender differences in the SOLVD trials: Several clinical differences were apparent between women and men enrolled in each trial. In both trials, men had a higher prevalence of previous acute myocardial infarction: 82% men versus 69% women, prevention trial; and 69% men versus 56% women, treatment trial (p <0.001). Women enrolled in the treatment trial were more likely to have systemic hypertension: 55 versus 39% (p <0.001). The prevalence of diabetes mellitus and systemic hypertension was higher among all women enrolled (trials combined): 26% women versus 18% men (p <0.001). In both trials, women were less likely to have undergone previous coronary artery bypass grafting: 16% women versus 31% men, prevention trial; 14% women versus 25% men, treatment trial (p <0.001). In both trials, more men had a diagnosis of ischemic disease than women: 84% men versus 74% women, prevention trial; 74% men versus 61% women, treatment trial; p <0.001. Differences in coronary artery bypass grafting between men and women remained in both trials, after controlling for clinical site variation and presence of ischemic heart disease. When limited to patients with coronary artery disease, women underwent bypass surgery less frequently than men in both the prevention (28 vs 41%; p <0.001) and the treatment (24 vs 30%; p <0.001) trials. More women had an etiology of LV dysfunction characterized as "unknown": 16% women versus 9% men, prevention trial; 26% women versus 16% men, treatment trial; p <0.001.

Overall, for the combined trials women had dyspnea on exertion more than men: 59% women versus 48% men (p <0.001). Within the prevention trial, more women were in New York Heart Association class II than men: 40% women versus 32% men (p <0.001). Reciprocally, in the treatment trial, fewer women than men were in class I (6% women vs 12% men, p <0.001), indicating a trend in women toward more functional impairment. Within the treatment trial, more women (22%) than men (15%) had edema. No other gender differences were found within each trial, but when combined, women were more likely to have an S_3 gallop (17% women vs 11% men, p <0.001), and to have detectable elevation in the jugular venous pressure (17% women vs 5% men, p <0.001). Furthermore, more women overall and in each trial had cardiothoracic ratios >0.5: 51% women versus 37% men, prevention trial (p <0.001); and 65% women versus 53% men, treatment trial (p <0.001). Coinciding with the higher prevalence of edema among women in both trials, 23% of women versus 16% of men (p <0.001) in the prevention trial were taking a diuretic. In the treatment trial, women were more likely to be taking a loop diuretic: 80% women versus 74% men (p <0.001). Men in both trials were more frequently taking antiplatelet drugs at baseline (55% men vs 40% women in the prevention trial, and 35% men vs 27% women in the treatment trial [both differences p <0.001]), probably reflecting the greater prevalence of ischemic heart disease in men. Within the treatment trial, 24% of men compared with 15% of women were taking antiarrhythmic agents (p <0.001).

Race differences in the SOLVD trials: In both trials, Caucasians had a higher prevalence of previous myocardial infarction: 83% Caucasians versus 58% non-Caucasians, prevention trial; and 69% Caucasians versus 51% non-Caucasians, treatment trial (p <0.001). Both systemic hypertension and diabetes mellitus were more prevalent in non-Caucasians in both trials. Overall (trials combined), 57% of non-Caucasians versus 36% Caucasians (p <0.001) had hypertension, and 30% non-Caucasians versus 17% Caucasians (p <0.001) had diabetes. In both trials, non-Caucasians were less likely to have undergone previous coronary artery bypass grafting: 16% non-Caucasians versus 32% Caucasians, prevention trial; 12% non-Caucasians versus 26% Caucasians, treatment trial (p <0.001). When limited to patients with ischemic heart disease, non-Caucasians underwent bypass surgery less frequently in both the prevention (29 vs 41%; p <0.001) and treatment (19 vs 31%; p <0.001) trials. In both trials, more Caucasians had a diagnosis of ischemic heart disease than non-Caucasians: 86% Caucasians versus 64% non-Caucasians, prevention trial; 76% Caucasians versus 53% non-Caucasians, treatment trial (both p <0.001). In the combined trials, "other specific" causes of LV dysfunction were more likely present in non-Caucasians (18%) than in Caucasians (6%) (p <0.001).

Within each trial, there was little difference in clinical findings between Caucasians and non-Caucasians. In the trials combined, non-Caucasians were more likely to have S_3 heart sound (18 vs 11%), elevated jugular venous pressure (9 vs 5%), x-ray evidence of pulmonary venous congestion (15 vs 12%), and a cardiothoracic ratio >0.5 (57 vs 44%) (all p <0.001). More Caucasions were taking β blockers (19 vs 11%, p <0.001) and antiplatelet drugs (49 vs 31%, $p < 0.001$) than non-Caucasians, perhaps reflecting the increased prevalence of ischemic heart disease in Caucasians.

DISCUSSION

SOLVD was designed to evaluate the effects of enalapril on long-term mortality in patients with severe LV dysfunction. By relying on entry criteria primarily based on age and LV ejection fraction, and including patients from a wide geographic area (United States, Canada and Belgium), the resultant sample provides a description of the clinical characteristics found in patients with LV dysfunction. Moreover, the unique design features of the SOLVD protocol resulted in characterization of 2 subgroups of patients with severe LV dysfunction. Patients with symptoms or requiring therapy for heart failure; or both, were enrolled in the treatment trial, whereas patients with few or absent symptoms and not receiving therapy for LV dysfunction were eligible for the prevention trial. This report, by presenting the data that characterize the patients in the SOLVD trials, will allow readers to determine whether the results of the studies can be generalized to patients with LV dysfunction seen in clinical practice.

The primary cause of LV dysfunction in both SOLVD trials was ischemic heart disease. This is in contrast to the dominance of systemic hypertension as a primary etiologic factor in the Framingham Study,[4] which preceded CHF in 75% of cases. In Framingham patients, coronary artery disease was found in only 39%, and was frequently accompanied by systemic hypertension. Similar findings were observed in a Swedish community-based study.[3] In patients who developed CHF in 17 years of follow-up, the prevalence of systemic hypertension was 43%, whereas myocardial infarction was less, 36%. The methods used to identify eligible SOLVD patients likely accounted for the differences in prevalence of hypertension and coronary artery disease in this population. In contrast to the aforementioned 2 community-based studies,[3,4] SOLVD was primarily hospital-based, and relied extensively on screening LV ejection fractions to identify patients. The nature of patient identification procedures may have also influenced the incidence of ischemic heart disease and prior myocardial infarction in the 2 trials. In particular, asymptomatic patients were unlikely to be identified unless they had a prior myocardial infarction. Ischemic heart disease, however, remained the dominant cause of LV dysfunction after separating prevention trial patients into those with or without recent myocardial infarction.

The association of diabetes mellitus and systemic hypertension with LV dysfunction, first established by the Framingham group,[4] was further confirmed in our patients. The possibility that both diabetes mellitus and systemic hypertension may be linked to LV dysfunction independent of their respective roles as risk factors for ischemic heart disease is suggested by our baseline data. Proportionately, treatment trial patients were less likely to have the primary diagnosis of ischemic heart disease than prevention trial patients, yet were more likely to have diabetes mellitus and systemic hypertension. A similar trend was seen in women, fewer of whom had a history of infarction; however, 49% had a history of systemic hypertension and 26% had coexisting diabetes mellitus. These observations may also help explain the tendency to label more treatment trial patients in the "unknown etiology" category. Possible contributing factors to the higher percentage of treatment trial women described as having "unknown" etiology for LV dysfunction are the higher incidence of systemic hypertension and the association of postpartum cardiomyopathy. Patients with no evidence of coronary artery disease and an associated identifiable cause of LV dysfunction accounted for <10% of SOLVD patients and were listed as "other" (Table I).

The relation of gender and race to clinical presentation in LV dysfunction was examined by analyzing the data from patients in both SOLVD trials and from the trials combined. Women more frequently manifested the symptoms and signs most often associated with CHF and appeared to have greater functional impairment for comparable levels of LV systolic dysfunction. This difference was not accounted for by the increased number of women in the treatment trial, since women in both trials had more symptoms than their male counterparts. Gender and race appeared to have influenced whether SOLVD patients had undergone coronary bypass surgery. Despite coronary artery disease being the major cause of LV dysfunction in both groups, fewer women and non-Caucasians had undergone previous coronary artery surgery. Although no attempt was made to control for all the possible confounding variables, the differences based on gender and race remained significant after controlling for clinical centers (variability from recruitment on other demographic sources) and stratification based on the presence of ischemic heart disease. A similar trend of decreased use of bypass surgery in women has been noted in previous studies.[11,12]

The difficulty in establishing a classification system that precisely defines the severity of CHF has previously been reviewed.[13] The New York Heart Association classification, widely used in clinical trials, has lacked reproducibility and validity when compared with more detailed methods.[14] As dictated by the protocol, treatment trial patients had more objective indexes of greater LV dysfunction. Although highly significant from a statistical point of view, the mean ejection fraction of the 2 groups was separated by only 3%. Although various "cut points" for LV ejection fraction have been proposed at which level patients can be segregated into high and low risk groups,[15,16] other variables should be considered. Clinical findings representing diastolic dysfunction (jugular venous distension, presence of a third heart sound or pulmonary congestion on x-ray) were more frequent in treatment trial patients, highlighting the interplay between symptomatic status and underlying abnormalities of cardiac function.

Based on the difficulty in stratifying patients with varying degrees of LV dysfunction, it is important to examine the possibility of overlap between patients in the prevention and treatment trials. From the perspective of LV ejection fraction, proportionately more treatment trial patients had ejection fractions in the lower quintiles, whereas more prevention trial patients occupied the upper quintile. As expected, signs and symptoms of CHF (presence of an S_3, elevated jugular venous pressure or pulmonary vascular congestion) were present in 4 times as many patients in the treatment trial than in patients in the prevention trial. Moreover, treatment trial patients in both New York Heart Association classes I and II were approximately 2½ times more likely to have one of these variables present, relative to class I and II patients in the prevention trial. Finally, in a SOLVD substudy we have recently demonstrated a stepwise increase in neurohormonal abnormalities, with treatment trial patients having more indexes of neurohormonal activation than either age-matched controls or prevention trial patients.[17] The differences observed in clinical findings between prevention and treatment trial patients tend to support the original concept that SOLVD represents 2 separate but concurrent trials, enrolling different populations.

The number of medications required by SOLVD patients reflects the number and complexity of diseases associated with LV dysfunction. Patients in the treatment trial required more cardiovascular medications than those in the prevention trial. Over half of the patients in either trial had a history of angina pectoris; the relative popularity of calcium antagonists over β blockers in SOLVD patients raises some concern because of recent evidence suggesting caution when using calcium antagonists in patients with LV dysfunction.[18] The known association of advanced ventricular arrhythmias in patients with LV dysfunction[19] was reflected in the use of antiarrhythmic medications in both trials. The potential for both proarrhythmia and worsening CHF due to antiarrhythmic therapy in LV dysfunction has been demonstrated by several groups.[20,21] The number of cardiovascular medications required by SOLVD patients highlights the need for newer medications for CHF not to interact adversely with other drugs used in patients with LV dysfunction.

Finally, the description of clinical baseline characteristics of patients in the SOLVD trials likely represents a partially restricted view of the total spectrum of patients with LV dysfunction. Enrolled patients in SOLVD represented only 12% of potentially eligible patients based on age and LV ejection fraction criteria (Figure 1). To broaden this view, a registry has enrolled a further 6,336 patients with the primary objective of studying the influence of clinical characteristics on mortality. The interaction of the clinical baseline characteristics described in this report with response to therapy and effects on survival, as well as the overall comparison with those obtained in the SOLVD Registry will be reported in subsequent SOLVD publications.

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Prevalence of Anticardiolipin Antibody in Isolated Mitral or Aortic Regurgitation, or Both, and Possible Relation to Cerebral Ischemic Events

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Anticardiolipin antibodies (acLa) are associated with a thrombotic tendency (often involving cerebral ischemic events), are frequently present with systemic lupus erythematosus and have been found together with cardiac valve abnormalities. Previous studies evaluated patients characterized by the presence of acLa or lupus, precluding assessment of the frequency of acLa in those with valvular disease. This study aims to establish the prevalence of acLa in patients with valve disease in the absence of lupus and, furthermore, to determine the influence of acLa on the risk of cerebral events in valve disease. Eighty-seven consecutive patients with mitral or aortic regurgitation, or both, prospectively underwent enzyme-linked immunosorbent assay testing for immunoglobulin G (IgG) and M acLa, as did 24 normal subjects. AcLa values ≥ 3 SD above the normal mean were considered "positive." Prior cerebral events were defined retrospectively. Of 87 patients with valvular disease, 26 had positive IgG acLa levels compared with 0 of 24 normal subjects ($p < 0.01$). AcLa values did not vary with valve disease etiology. Focal cerebral events had occurred in 8 patients and were embolic or probably embolic in 7, including 7 of 26 IgG acLa-positive and 1 of 60 IgG acLa-negative patients ($p < 0.001$). In the absence of lupus, IgG acLa is highly prevalent among patients with aortic or mitral regurgitation, or both; this association may indicate a relatively high risk for cerebral emboli.

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In several recent reports, patients with anticardiolipin antibodies (acLa) both with[1-3] and without[4-6] systemic lupus erythematosus manifested a relatively high prevalence of valvular abnormalities. However, these studies were uniformly performed in patients selected on the basis of abnormal serum acLa concentrations. The prevalence of acLa in patients with valvular abnormalities with or without lupus has not been defined either retrospectively or prospectively. An association between valvular disease and acLa is potentially important; particularly when they are of the immunoglobulin G (IgG) isotype, these antibodies are associated with a thrombotic tendency.[7] In patients with cerebral ischemic events, an association between acLa and valvular heart disease has been suggested by case reports and small series,[8-10] including our recent retrospective analysis of 21 patients with acLa and focal neurologic events.[11] To define the prevalence of acLa in patients with valvular disease, we prospectively assessed acLa in a cohort with well-defined mitral or aortic regurgitation, or both, in the absence of systemic lupus erythematosus. Furthermore, using retrospective analysis, we sought preliminary evidence of an influence of acLa on the association of cerebral ischemic events in patients with valvular disease.

METHODS

Patients with valvular heart disease: Eighty-nine consecutive patients who presented with hemodynamically important, isolated aortic or mitral regurgitation, or both, due to valvular causes were assessed for presence of acLa of the IgG or immunoglobulin M (IgM) isotypes; 29 patients had undergone valve replacement or repair. Patients were part of an ongoing prospective assessment of prognostic indexes in regurgitant valve disease, which they had entered between 1981 and 1990. For entry in the prognostic study, patients had to be aged <75 years, with evidence of severe mitral or aortic regurgitation, or both, documented by cardiac catheterization or a combination of physical findings and echocardiographic observations, as previously described.[12-14] Patients were excluded from entry if valve replacement was performed before the initial objective testing. No patient was referred to the study in the context of a cerebral ischemic event, 2 had history of such an event, 1 had an event during the year of entry, and only 1 was known to have had an ischemic event at the time of entry. Other events were noted retrospectively in the context of the present study. (The presence or absence of a cerebral ischemic event was not the basis for inclusion or exclusion of patients from the prognostic

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TABLE I Increased Anticardiolipin Antibodies as a Function of Valvular Disease Etiology

Etiology	No. of Pts.	IgG with IgM	IgG With or Without IgM (%)
Rheumatic	21	2	7 (33)
Mitral valve prolapse	24	1	6 (25)
Congenital	12	0	3 (25)
Other	30	3	10 (33)
Total	87	6	26 (30)

No significant differences were found between different groups.
Congenital = congenital valve disease; IgG = immunoglobulin G; IgM = immunoglobulin M; Other = Marfan syndrome, ankylosing spondylitis, healed infective endocarditis, idiopathic aortic root dilatation or other idiopathic; Rheumatic = rheumatic valvular disease, definite or probable.

TABLE II Increased Anticardiolipin Antibodies as a Function of Valve Involved

Valve Lesion	No. of Pts.	IgG with IgM (%)	IgG With or Without IgM (%)
Isolated AR	44	2 (4)	11 (25)
Isolated MR	31	1 (3)	6 (19)
AR and MR	12	3 (25)	9 (75)
Total	87	6 (7)	26 (30)

For IgG with or without IgM: AR vs AR & MR, $p < 0.01$; and MR vs AR & MR, $p < 0.001$. For IgG with IgM: AR vs MR vs AR & MR, $p < 0.05$.
AR = aortic regurgitation; MR = mitral regurgitation; other abbreviations as in Table I.

study.) Refusals of patients to participate in the prognostic study were infrequent. Thus, the prognostic study cohort can be considered representative of the group of patients presenting with regurgitant valvular disease to an urban tertiary referral center. The study cohort represents a subset of the larger study population, selected on the basis of almost consecutive presentation at New York Hospital for the protocol-mandated annual evaluation. At the time of evaluation, most patients clinically had no cardiac-related symptoms; 73 were in New York Heart Association functional class I, 14 were in class II, and none were in class III or IV. As per protocol restrictions for entry in the regurgitant valve study, patients with evidence of previous myocardial infarction or typical angina pectoris were excluded. We also excluded patients if they had any systemic disease that could confound or affect the acLa determination, such as lupus erythematosus or lymphoproliferative disorders, or if they were receiving any treatment (such as corticosteroids) that could potentially suppress an existing acLa. This resulted in exclusion of 2 patients who were part of the larger prognostic study. Serum antinuclear antibody determinations were obtained in each study subject. Two patients were receiving steroids at the time of assessment and thus were excluded from subsequent analysis, leaving a study cohort of 87 patients. The apparent etiology of valvular disease is presented in Table I, which reveals a broad spectrum of etiologies.

Normal subjects: Twenty-four healthy subjects without history of cardiac disease and with normal echocardiograms were included. Control subjects were similar to patients with valvular disease in age (controls: 36 to 58 years, mean 46, and patients: 29 to 78 years, mean 52; p = not significant [NS]) and sex (women: men = 1:1.4 vs 1:1.8, controls vs patients, respectively; p = NS). M-mode, 2-dimensional and Doppler echocardiograms were obtained to exclude valvular regurgitation, stenosis or structural abnormality, including leaflet prolapse.

Anticardiolipin antibody assay: Serum acLa level was assayed by 1 investigator according to the enzyme-linked immunosorbent assay method, as previously described,[15] with quantification of both the IgG and IgM subfractions. A "positive" reading for either isotype was considered ≥3 SD above the mean normal value.

Criteria for diagnosis of ischemic events: Information regarding cerebral ischemic events was obtained from each patient by 1 investigator. Historical information from the patient was supplemented by neurologic and physical examinations, review of hospital charts, office notes of primary physicians, reports of computerized tomographic images, and direct review of magnetic resonance images (when available). Transient ischemic events were defined as focal ischemic neurologic events lasting <24 hours, and strokes were defined as focal ischemic neurologic events lasting >24 hours. Sudden monocular visual loss of any duration was defined as ocular ischemia. The diagnosis of a cerebral ischemic event and the type of event were independently determined by 2 investigators or, in 2 cases, 2 investigators and 1 other staff neurologist. In all 8 patients with ischemic events, concordance was found in diagnosis and type of event among all neurologists. The time elapsed between the most recent cerebral ischemic event and acLa testing varied from 0 to 6 years (mean 3).

Data analysis: The chi-square test was used to determine significant associations between variables. The Fisher exact test was used when assumptions for the chi-square test were not fulfilled. All tests were evaluated at the 5% level.

RESULTS

The distribution of diagnostic acLa increases according to valve lesion and immunoglobulin subclass is presented in Table II. Distribution of acLa values (optical density) among patients and normal subjects is presented in Figure 1. The difference in proportions of acLa IgG levels between normal subjects and patients with valvular disease was highly significant (p <0.01; Figure 1). The IgM acLa distribution was parallel to that of IgG among patients and normal subjects, but the difference between the 2 groups did not reach statistical significance.

IgG acLa positivity was significantly associated with abnormalities of both aortic and mitral valves in the same patient (p <0.01 and <0.001 compared with isolated aortic and mitral disease, respectively; Table II). A relation was also observed between the number of valves involved and positivity of both IgG and IgM (p <0.05; Table II); however, pairwise comparisons between 1- and 2-valve involvement did not reach statistical significance. There was no significant association of acLa with a specific etiology for valvular disease (Table I). Similarly, no etiology-specific association was apparent for IgM acLa.

There was no significant association between acLa positivity and valve replacement or repair: 6 of 26 patients with and 20 of 61 without valve surgery were IgG acLa-positive, and 3 of 26 with and 10 of 61 patients without valve surgery were IgM acLa-positive. Similarly, atrial fibrillation was not associated with acLa prevalence; 4 of 14 patients with atrial fibrillation had increased IgG acLa compared with 22 of 73 in sinus rhythm (p = NS), and 1 with atrial fibrillation had increased IgM acLa compared with 12 in sinus rhythm (p = NS). Twenty of 86 patients had low-level antinuclear antibody (ANA) positivity (including 3 patients with 1 other American Rheumatology Association criterion for the diagnosis of lupus who therefore by definition were considered to have a "lupus-like illness,"[16] although none fulfilled diagnostic criteria for lupus). There was no relation between ANA and acLa positivity.

Focal cerebral ischemic events: Ten of 86 evaluable patients had history of focal neurologic deficits or ocular ischemia (information was not available in 1 patient). Two patients had transient neurologic deficits in association with infectious endocarditis, and 8 (9%) had ischemic events. Mean age at the time of ischemic events was 49 years (range 28 to 63).

Of 8 patients who had ischemic events, 5 had irreversible lesions (4 strokes and 1 ocular ischemia); multiple strokes affected 2 patients. Events were embolic in 3 of 4 patients with stroke, and probably embolic in the fourth who subsequently was found to have noninfectious aortic and mitral valve vegetations. Findings in the patient with retinal ischemia also suggested embolic etiology. The remaining 3 patients had transient focal ischemic events, occurring in multiple episodes in 2. Embolic events clearly had occurred in 2 patients with transient events.

There were noncardiac risk factors for stroke in 2 of 8 patients with focal ischemic events (smoking and hypertension, the latter associated with noninfectious valvular vegetations at the time of a second stroke). Neither atrial fibrillation nor preexisting valve prostheses were significantly associated with focal ischemic events. All 4 acLa-positive patients with stroke were in sinus rhythm at the time of the first event; no patient with

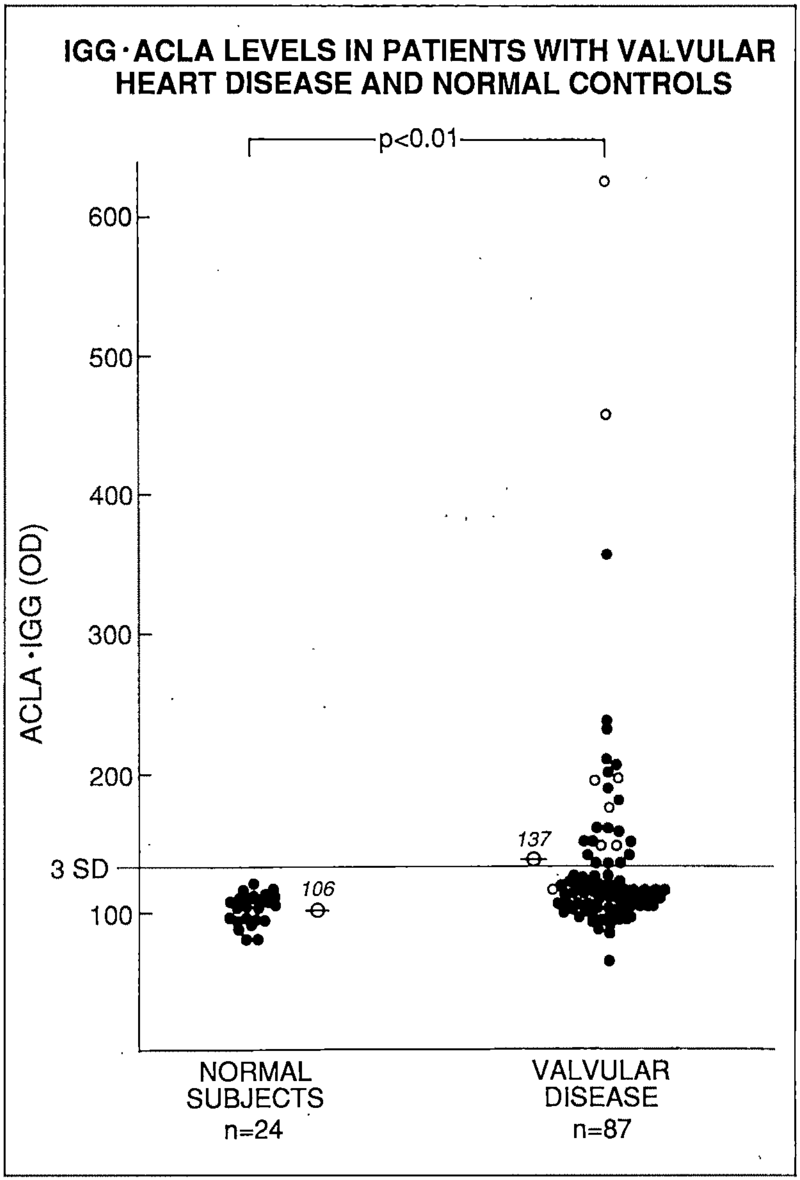

FIGURE 1. ***Open circles*** **are patients with cerebral ischemic events;** ***closed circles*** **are those without cerebral ischemic events. ACLA = anticardiolipin antibody; IGG = immunoglobulin G; OD = optical density (assay units); -⊖- = mean value.**

transient ischemic events or ocular ischemia had atrial fibrillation. No acLa-positive patient with stroke had undergone valve replacement before the initial stroke event; only 1 acLa-positive patient with transient ischemic events had undergone valve replacement before the initial neurologic event.

Relation of anticardiolipin antibodies and prior ischemic events: Among 8 patients who had had cerebral ischemic events, 7 (87%) had increased IgG acLa (1 with accompanying increased IgM, all with aortic regurgitation, and 4 also manifesting mitral regurgitation). Embolic events were diagnosed in 5 of these patients and were possibly present in a sixth patient, in all cases in the absence of atrial fibrillation or preceding valve replacement before the first ischemic event. Significant noncardiac risk factors for stroke were absent in all but 1 of these patients. The 1 acLa-negative patient had recurrent unilateral ocular ischemia, initially occurring before valve replacement. Thus, cerebral ischemic events occurred in 7 of 26 IgG acLa–positive patients (27%) and in 1 of 60 evaluable patients without diagnostic IgG acLa increases ($p < 0.001$). This highly significant difference was not altered when IgG or IgM acLa abnormalities were considered together, nor when the more conservative cut point of 5 SD above the normal mean was used ($p = 0.03$). No relation was apparent between ANA positivity and cerebral ischemic events (ANA positive in 4 of 8 patients with events and in 16 of 78 without events; p = NS).

DISCUSSION

The results of this study indicate that in the absence of systemic lupus erythematosus, the IgG isotype of acLa is found relatively frequently among patients with regurgitant valvular heart disease. Furthermore, the data indicate that the prevalence of acLa is similar over a wide range of valve disease etiologies.

Several previous reports[1,17–20] described valvular abnormalities in patients with lupus who also manifest acLa or the closely related lupus anticoagulant.[21,22] Recently, Khamashta et al[2] used echocardiography to survey 132 consecutive patients with systemic lupus erythematosus and found valvular abnormalities among 42% of those with and 13% of those without an acLa.[2] This study is supported by many case reports and small series[1,17–20] suggesting an association between cardiac valvular abnormalities and acLa among patients with lupus. An association between acLa and valvular disease has also been found in the absence of lupus.[4–6,11] Most recently, Galve et al[5] reported valve abnormalities in 10 of 28 consecutive patients manifesting acLa without lupus.[5] However, no previous study surveyed patients selected specifically for valve disease, rather than for lupus or acLa, or both. Thus, the frequency of acLa in patients with valvular disease was not previously appreciated.

The relative frequency of ischemic neurologic events represents the most striking concomitant of the association between acLa and valvular disease. In the series of Khamashta et al,[2] 9 of 30 patients with lupus and valvular abnormalities had cerebrovascular events, but the relation of these events to acLa was not reported. However, several previous case reports and retrospective series suggested a relation between ischemic neurologic events and lupus anticoagulant or acLa, even in the absence of lupus.[1,3,8,9,18,20,23–27] Furthermore, our own retrospective series linked this association with valvular disease,[11] a finding supported by previous, isolated case reports[9,17,19,20,23–26,28] and the retrospective series of Chartash et al[1] and Asherson et al.[8]

No previous series selected only for valvular disease demonstrated association of ischemic neurologic events with the subgroup manifesting acLa. The present series suggests such association. However, the strength of this conclusion is mitigated by the fact that the neurologic events in our patients occurred before obtaining acLa measurements, before the formulation of the series, and were relatively few in number, despite their significant segregation. Thus, the association can be regarded only as a preliminary observation. However, most events in our patients appeared to be embolic. This is also consistent with our earlier retrospective findings[11] and the proclivity for thromboembolic events among acLa-positive patients recovering from myocardial infarction, as reported by Hamsten et al.[29] These findings suggest the possibility of an important pathophysiologic relation between acLa, valvular disease and embolic stroke in the absence of lupus.

The data suggest that the IgG subtype of acLa is most clearly associated with valvular disease and the proclivity for development of neurologic events. The IgM subtype was far less frequently present. Furthermore, the concomitance of IgM acLa positivity did not significantly alter the relation between IgG acLa and valvular disease or neurologic events. These findings differ somewhat from those that would be expected on the basis of the data of Cronin et al,[10] who found that among patients with systemic lupus erythematosus and complicating events including thromboses, valvular disease was more frequent when both IgG and IgM acLa were present than when IgG acLa alone was found. The reason for this discrepancy is unclear, although other factors associated with lupus may have modified the relation between the antibody subtypes and cardiac valves.

The data suggest but do not prove that among patients with valvular disease and without lupus, the presence of clearly abnormal levels of acLa represents a significant risk factor for embolic neurologic events. Although the retrospective data do not permit inferences regarding causality, this finding suggests the potential prophylactic use of pharmacologic antiembolic therapy in patients manifesting both valvular disease and acLa. Further studies are needed to determine whether such prophylactic therapy can reduce the risk of neurologic ischemic events with acceptable safety.

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Effects of Calcitonin Gene-Related Peptide on Cardiac Contractility, Coronary Hemodynamics and Myocardial Energetics in Idiopathic Dilated Cardiomyopathy

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This study was performed to examine the effects of calcitonin gene-related peptide on cardiac function and coronary circulation in patients with heart failure. Synthetic human calcitonin gene-related peptide was infused in the left main coronary artery of 9 patients undergoing cardiac catheterization at different doses corresponding to incremental infusion rates of 15, 50, 150 and 600 pmol · min^{-1}. No hemodynamic change was observed in response to administration of the 2 lowest doses. The 2 highest doses induced an increase in cardiac index and a decrease in systemic arterial pressure. The infusion of 600 pmol · min^{-1} resulted in a decrease of mean systemic arterial pressure (86.8 ± 6.5 to 71.8 ± 4.9 mm Hg; $p < 0.01$), and an increase in both cardiac index (2.1 ± 0.1 to 3.1 ± 0.17 liters · min^{-1} · m^{-2}; $p < 0.01$) and heart rate (87 ± 3.7 to 101 ± 6.1 beats · min^{-1}; $p < 0.01$). These hemodynamic changes were associated with a significant increase in plasma norepinephrine and epinephrine concentrations. Peak positive first derivative of left ventricular pressure did not change at any infusion rate. Left ventricular end-diastolic pressure decreased at the 2 highest doses associated with a decrease in plasma atrial natriuretic factor concentration (730 ± 140 to 436 ± 115 pg · ml^{-1}; $p < 0.05$). Coronary blood flow increased only for the 2 highest doses (122 ± 11.2 to 148 ± 14.3 and 174 ± 19.2 ml · min^{-1}, respectively; $p < 0.01$), whereas coronary resistance decreased (0.64 ± 0.08 to 0.32 ± 0.04 and 0.36 ± 0.04 mm Hg · ml^{-1} · min, respectively; $p < 0.01$). Myocardial oxygen consumption remained unchanged for any doses of the peptide. These results show that in patients with heart failure, calcitonin gene-related peptide has no direct effect on cardiac contractility. Therefore, in patients with heart failure, beneficial hemodynamic effects of exogenous calcitonin gene-related peptide during short-term infusion is probably related to its vasodilatory properties.

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Many data suggest that calcitonin gene-related peptide may be a cardiac neurotransmitter and mediate the effects of nonadrenergic, noncholinergic nerves.[1-3] In human studies, both vasodilator and positive inotropic actions of calcitonin gene-related peptide have been reported, suggesting that it could exert beneficial effects especially in patients with congestive heart failure. In normal subjects, the intravenous administration of calcitonin gene-related peptide is associated with systemic hypotension, chronotropic and inotropic effects, and increased plasma norepinephrine and epinephrine levels.[4-8] When examining in normal hearts the responses to intracoronary infusion of calcitonin gene-related peptide, marked dilation of epicardial coronary arteries was observed.[9] In patients with congestive heart failure, infusion of the peptide has been shown to induce systemic vasodilation, increase cardiac output and improve myocardial contractility.[10-12] However, in these studies the peripheral vasodilation induced by the peptide infusion may have overriden a direct action on cardiac function. The present study was performed to delineate the effects of calcitonin gene-related peptide on the coronary hemodynamics, myocardial contractility and energetics of failing human hearts. By infusing the peptide in the left main coronary artery, cardiac effects and coronary vascular changes were expected to be studied without any major change in loading conditions. Because in experimental studies calcitonin gene-related peptide has been found to increase atrial natriuretic factor release, which could have additional vascular action, the influence of calcitonin gene-related peptide infusion on plasma concentrations of atrial natriuretic factor was examined, and plasma concentrations of catecholamines were also determined.

METHODS

Patients: Nine patients (7 men and 2 women, age range 31 to 62 years, mean 43 ± 17) with congestive heart failure related to idiopathic dilated cardiomyopathy participated in this study. Patients were in New York Heart Association functional class II or III and had symptoms of congestive heart failure for >6 months. End-diastolic diameter was enlarged (mean 66 ± 18 mm), as documented by echocardiographic measurements. Because no other recognized etiology was present, the cause of heart failure was considered to be related to idiopathic dilated cardiomyopathy. All patients had normal coronary arteries on the coronary angiogram. Patients were in sinus rhythm, and their left

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TABLE I Patient Characteristics, and Hemodynamic Response to Calcitonin Gene-Related Peptide (CGRP) Infusion (600 pmol · min^{-1}) in Patients with Congestive Heart Failure

Pt. No.	LVEF (%)	HR (beats/min)		LVEDP (mm Hg)		MAP (mm Hg)		MRAP (mm Hg)		CI (L · min^{-1} · m^{-2})		SVR (mm Hg · L^{-1} · min)		A-VO$_2$D (ml · 100 ml^{-1})		LV dP/dt (mm Hg · s^{-1})	
		B	M	B	M	B	M	B	M	B	M	B	M	B	M	B	M
1	35	89	100	10	9	105	84	14	11	2.42	2.84	19.78	13.53	4.1	2.3	1,020	1,040
2	15	101	125	26	13	74	56	10.5	7	1.78	3.62	20.48	7.78	3.9	2	720	800
3	15	93	92	36	28	103	96	10	10	2.33	3.67	20.66	12.11	7.1	5.8	560	720
4	25	65	80	5	4	70	60	4	2	2.18	2.93	18.85	12.34	4.5	3	900	1,200
5	10	79	98	25.5	15.5	56	55	12.5	10	1.94	3.05	12.43	8.18	4.3	4.1	330	450
6	27	82	91	8	8	104	85	10.5	10.5	1.94	2.62	27.50	16.29	4.8	3.8	820	960
7	15	93	137	18	9	68	68	8	8	1.78	2.44	17.14	12.5	6.6	4.9	460	560
8	22	81	86	11	2	106	62	9	8	2.02	2.77	32.33	13.17	4.3	3.7	600	400
9	32	99	100	25	10	96	80	11	7	2.65	3.95	18.08	10.43	3.8	2.9	920	960
Mean	21.8	87.0	101.0	18.3	10.9	86.8	71.8	10	8.17	2.1	3.10	20.81	11.8	4.80	3.60	710	788
±SE	±2.8	±3.7	±6.1	±3.5	±2.5	±6.5	±4.9	±1	±0.90	±0.1	±0.17	±1.95	±0.9	±0.39	±0.36	±81	±92
p value		<0.01		<0.01		<0.01		<0.05		<0.01		<0.01		<0.01		NS	

A-VO$_2$D = arteriovenous oxygen difference; B = baseline values; CI = cardiac index; HR = heart rate; LV dP/dt = first derivative of peak positive left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; M = 600 pmol · min^{-1} CGRP infusion rate; MAP = mean arterial pressure; MRAP = mean right atrial pressure; NS = not significant; SVR = systemic vascular resistance.

ventricular ejection fraction was 21.8 ± 8.6%. Patients were treated with captopril (75 to 150 mg/day) and diuretics (furosemide, 20 to 80 mg/day), but with no digitalis, other inotropic agents or β blockers. All cardiac drugs were discontinued 48 hours before beginning the study. Patient fasted $\geq$12 hours before beginning the procedure. The protocol was approved by the ethical committee of Henri Mondor Hospital, and each patient gave informed written consent.

Catheterization procedure: The following different catheters were used: a 7Fr Swan-Ganz thermodilution catheter (Edwards Laboratory, Irvine, California) in the pulmonary artery through a femoral vein to determinate cardiac output (cardiac output computer 9520 A, Edwards Laboratory); a 7Fr coronary sinus thermodilution catheter (Wilton Webster Laboratories, Altadena, California) in the coronary sinus through the femoral or jugular vein to measure coronary sinus blood flow; a 5Fr micro-tip catheter transducer (Millar Industries, Houston, Texas) in the left ventricle through a femoral artery; and two 5Fr sheaths in the other femoral artery to introduce a 5Fr Judkins left coronary catheter and monitor arterial pressure.

Study protocol: After positioning the catheters, a 15-minute period was observed to ensure hemodynamic stabilization. Isotonic saline solution was infused in the left main coronary artery for 10 minutes at a rate of 1 ml · min^{-1} that corresponded to the conditions used for subsequent drug infusions. Baseline hemodynamic measurements were obtained during this time period.

Calcitonin gene-related peptide infusion: Synthetic human calcitonin gene-related peptide (Novabiochem, Laüfelfingen, Switzerland) was diluted in saline solution and infused in the left main coronary artery at incremental rates of 15, 50, 150 and 600 pmol · min^{-1} during 4 consecutive 5-minute periods. Because of the long half-life of calcitonin gene-related peptide, no recovery period was observed. Given a theoretical coronary blood flow of 120 ml · min^{-1},[13] these infusion rates were assumed to provide final concentrations of approximately 10^{-10}, 5×10^{-10}, 10^{-9} and 5×10^{-9} M, respectively. Hemodynamic parameters were monitored at the end of each 5-minute infusion period.

Data analysis and calculations: The following measurements were recorded: heart rate, mean right atrial, mean arterial and left ventricular pressures and first derivative of left ventricular pressure (peak positive left ventricular dP/dt). Pressure tracings and derivative were read on a multichannel recorder (Gould TA 2000, Ballainvilliers, France). Cardiac output was determined by the thermodilution method. Cardiac index was calculated as the ratio of the cardiac output over the body surface area. Coronary sinus blood flow was determined by the thermodilution method after infusion of 1 ml · sec^{-1} of saline solution (TR 400, Baxter, Intensive Care Division, Maurepas, France). The following formulas were used to derive hemodynamic variables: systemic vascular resistance (mm Hg · min · liter^{-1}) as mean arterial − mean right atrial pressure/cardiac output; and coronary vascular resistance (mm Hg · min · ml^{-1}) as mean aortic − left ventricular diastolic pressure (calculated by planimetry of left ventricular diastolic pressure curve on 3 consecutive cycles)/coronary sinus blood flow. Blood samples were obtained from the femoral and pulmonary arteries and the coronary sinus to measure oxygen saturation. In addition, lactate concentration was determined in the coronary sinus. Myocardial oxygen consumption (ml · min^{-1}) was calculated as the difference between arterial and coronary sinus blood oxygen contents (ml · 100 ml^{-1}) times the coronary sinus blood flow.

Intracoronary dobutamine infusion: The contractile responsiveness of the heart to dobutamine was examined in a subset of 6 patients (patients 1, 2, 5 and 7 to 9). After calcitonin gene-related peptide administration, hemodynamic recovery occurred within 40 minutes. After hemodynamic parameters stabilized, dobutamine diluted in saline solution was infused in the left main coronary artery at incremental rates of 25, 50, 100 and 200 μg/minute during 4 successive periods of 5 minutes each. To avoid heart rate influence on peak positive left ventricular dP/dt, drug infusion was stopped if heart rate increased by >10%. Thus, the maximal inotropic response obtained was scored using the last hemodynamic recordings before a significant increase in heart rate.

Determination of plasma catecholamine and atrial natriuretic factor concentrations: Plasma norepinephrine and epinephrine levels and immunoreactive atrial natriuretic factor were measured from blood samples obtained from the femoral artery and the coronary sinus at baseline and during calcitonin gene-related peptide infusion. This was performed at each step of infusion for atrial natriuretic factor and at the highest infusion rate for catecholamine determination. Catecholamine concentrations were determined using radioenzymatic assays.[14] Atrial natriuretic concentrations were determined using a radioimmunoassay that was previously described.[15]

Statistical analysis: Data are presented as mean ± SEM. Analysis of variance for repeated-measures models was used to detect any overall effect of calcitonin gene-related peptide on each parameter. If analysis of variance showed an overall significant result, pairwise comparisons were performed using paired *t* tests. A p value <0.05 was considered significant.

RESULTS

Infusion of calcitonin gene-related peptide: HEMODYNAMIC MEASUREMENTS: Individual baseline hemodynamic values are listed in Table I. Hemodynamic effects of calcitonin gene-related peptide are shown in Figure 1. There was no hemodynamic change in response to the 2 lowest doses of the peptide. Its infusion at the rate of 150 pmol $\cdot$ min^{-1} induced an increase in cardiac index to 2.67 ± 0.18 liter $\cdot$ min^{-1} $\cdot$ m^{-2} (p <0.01) and a decrease in both mean aortic pressure to 80.4 ± 5 mm Hg (p <0.05) and left ventricular end-diastolic pressure to

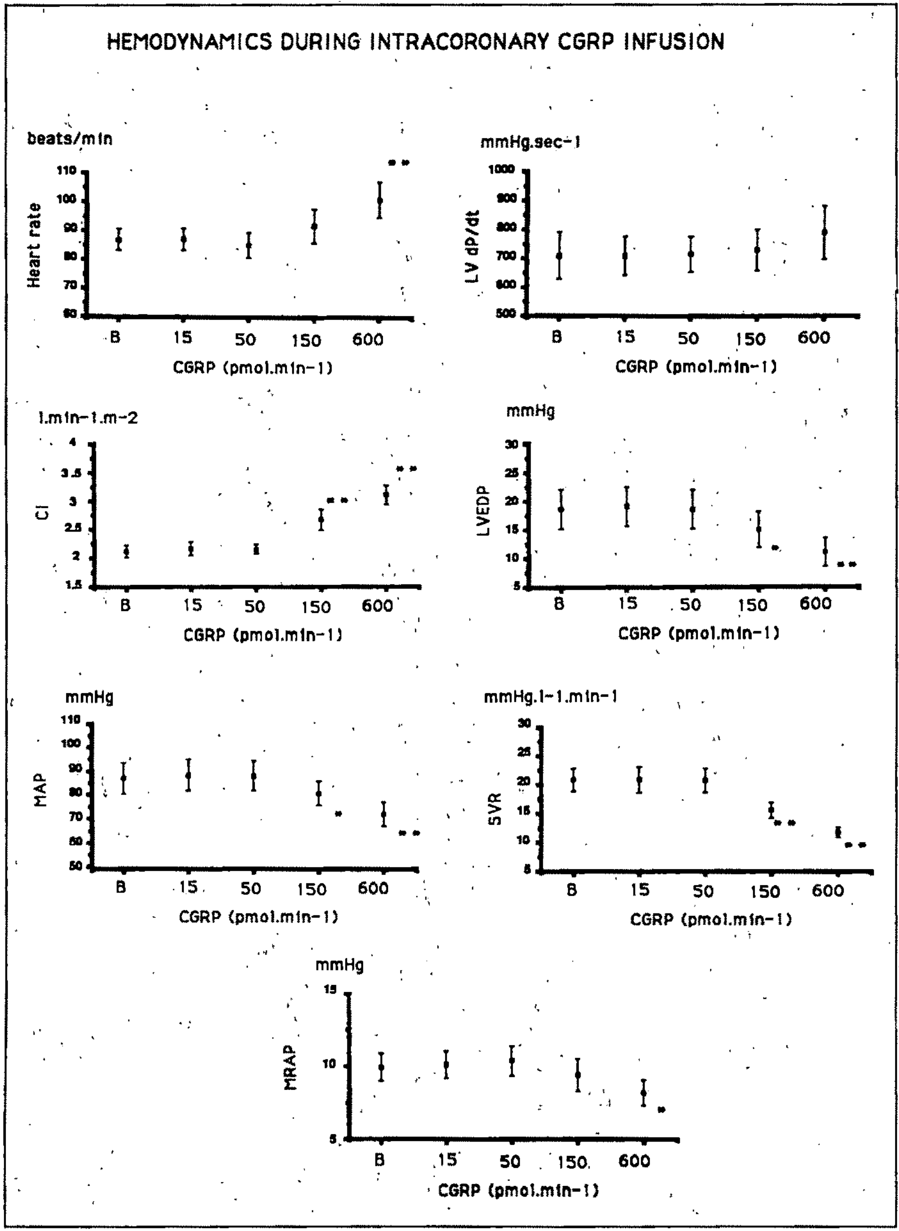

FIGURE 1. Hemodynamics improved at 2 highest intracoronary calcitonin gene-related peptide (CGRP) infusion rates, with increase in cardiac index (CI) and decrease in cardiac filling pressures. Left ventricular (LV) contractility remained unchanged. B = baseline; dP/dt = first derivative of pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; MRAP = mean right atrial pressure; SVR = systemic vascular resistance; *p <0.05; **p <0.01.

TABLE II Hemodynamics During Intracoronary Dobutamine Infusion

Pt. No.	LVEF (%)	HR (beats/min)		LVEDP (mm Hg)		MAP (mm Hg)		MRAP (mm Hg)		CI (L · min^{-1} · m^{-2})		SVR (mm Hg · L^{-1} · min)		LV dP/dt (mm Hg · s^{-1})	
		B	M	B	M	B	M	B	M	B	M	B	M	B	M
1	35	82	85	10	3	95	100	14	10	2.66	2.97	16	15.9	980	1,520
2	15	103	111	26	18	77	88	11	7	1.83	2.9	20.7	16	780	1,440
5	10	76	65	27	21	49	52	11	11	2.2	2.6	9.6	8.7	320	800
7	15	86	90	15	7	71	75	7	6	2	2.6	16.3	13.5	410	850
8	22	80	93	10	3	95	106	9.5	7	2.1	3.4	27.5	19.7	680	1,040
9	32	107	95	20	6	90	87	11	11	2.9	3.5	15.3	12.2	930	1,120
Mean	21.5	89.0	89.80	18	9.7	79.5	84.6	10.5	8.7	2.28	3.00	17.56	14.33	683	1,128
±SE	±4.1	±5.2	±6.12	±3	±3.2	±7.6	±7.9	±0.9	±0.9	±0.16	±0.15	±2.45	±1.54	±110	±121
p value		NS		<0.05		<0.05		<0.05		<0.05		<0.05		<0.05	

Abbreviations as in Table I.

TABLE III Coronary Hemodynamics Response to Calcitonin Gene-Related Peptide (CGRP) Infusion (600 pmol · min^{-1}) in Patients with Congestive Heart Failure

Pt. No.	CSBF (ml · min^{-1})		CR (mm Hg · ml^{-1} · min)		C-SO$_2$SAT (%)		CSO$_2$ (ml · 100 ml^{-1})		A-CSO$_2$D (ml · 100 ml^{-1})		MVO$_2$ (ml · min^{-1})	
	B	M	B	M	B	M	B	M	B	M	B	M
1	132	250	0.71	0.3	22.5	41.5	3	5.5	10.4	7.5	13.26	18.75
2	126	174	0.45	0.18	20.5	38.5	3.8	7.2	14	10.7	18.08	19.18
3	100	107	0.74	0.44	21.5	25.5	3.8	4.5	13.2	12.3	13.01	13.16
4	106	230	0.62	0.25	31	55	5.4	9.6	9.8	6.8	11.62	15.61
5	157	168	0.25	0.32	34.5	40	5	5.9	9.8	8.6	14.85	14.46
6	94	133	1.03	0.49	31.7	51	5.3	8.5	9.7	7.3	9.97	9.8
7	85	102	0.65	0.59	22	30.5	3.9	5.4	13.8	12.1	11.58	12.36
8	110	150	0.89	0.38	27	42.5	4	6.2	10.4	8	11.35	12.04
9	190	250	0.42	0.29	33	43	4.4	5.8	8.3	7.1	16.03	17.75
Mean	122.0	174.0	0.64	0.36	27.00	40.80	4.30	6.50	11.20	8.95	13.31	14.79
± SE	±11.2	±19.2	±0.08	±0.04	±1.85	±3.03	±0.27	±0.54	±0.67	±0.73	±0.86	±1.09
p value	<0.01		<0.01		<0.01		<0.01		<0.01		NS	

A-CSO$_2$D = arteriocoronary sinus blood oxygen difference; CR = coronary resistance; CSBF = coronary sinus blood flow; CSO$_2$ = coronary sinus blood oxygen content; C-SO$_2$SAT = coronary sinus oxygen saturation; MVO$_2$ = myocardial oxygen consumption; other abbreviations as in Table I.

15 ± 3 mm Hg ($p < 0.05$). Heart rate remained unchanged. At the highest infusion rate of 600 pmol · min^{-1}, heart rate increased to 101 ± 6.1 beats · min^{-1} ($p < 0.01$), cardiac index increased to 3.1 ± 0.17 liter · min^{-1} · m^{-2} ($p < 0.01$), whereas mean aortic and left ventricular end-diastolic pressures decreased to 71.8 ± 4.9 and 10.9 ± 2.5 mm Hg, respectively ($p < 0.01$).

LEFT VENTRICULAR CONTRACTILITY: At the 2 lowest calcitonin gene-related peptide doses, peak positive left ventricular dP/dt did not change, whereas heart rate and hemodynamics remained unchanged. At the 2 highest doses, peak positive dP/dt showed a slight but not significant increase. Before dobutamine infusion, hemodynamic values were similar to those recorded before calcitonin gene-related peptide administration (Table II). Dobutamine was infused at the rate of 200 μg · min^{-1} in 4 patients and at 100 μg · min^{-1} in 2 patients without any significant change in heart rate. At the maximal dobutamine infusion, peak positive left ventricular dP/dt increased by 65% ($p < 0.01$) (Table II).

CORONARY HEMODYNAMICS AND METABOLISM (TABLE III): At baseline, coronary sinus blood flow was 122 ± 11 ml · min^{-1}, coronary vascular resistance 0.64 ± 0.08 mm Hg · ml^{-1}, coronary sinus oxygen blood content 4.3 ± 3.03 ml · 100 ml^{-1} and sinus lactate concentration 1.94 ± 0.17 mmol · liter^{-1}. Coronary hemodynamic effects of calcitonin gene-related peptide are shown in Figure 2. The 2 lowest calcitonin gene-related peptide infusion rates of 15 and 50 pmol · min^{-1} changed neither coronary blood flow nor sinus oxygen content. In response to the infusion of 150 and 600 pmol · min^{-1} calcitonin gene-related peptide, coronary sinus blood flow increased to 148 ± 14.3 and 174 ± 19.2 ml · min^{-1}, respectively ($p < 0.01$), whereas coronary resistance decreased to 0.32 ± 0.04 and 0.36 ± 0.04 mm Hg · ml^{-1} · min, respectively ($p < 0.01$). These changes were associated with an increase in coronary sinus oxygen blood content to 6.0 ± 0.5 and 6.5 ± 0.54 ml · 100 ml^{-1}, respectively ($p < 0.01$). Coronary sinus lactate concentration decreased at the highest calcitonin gene-related peptide infusion rate to 1.53 ± 0.16 mmol · liter^{-1} ($p < 0.01$). Myocardial oxygen consumption remained unchanged at any calcitonin gene-related peptide infusion rate.

Hormonal concentrations: ATRIAL NATRIURETIC FACTOR CONCENTRATIONS (FIGURE 3): At baseline, plasma atrial natriuretic factor concentrations were 730 ± 140 pg · ml^{-1} in the peripheral artery and 2,889 ± 328 pg · ml^{-1} in the coronary sinus. There was no change in plasma atrial natriuretic factor concentration at 15 and

50 pmol · min^{-1} of calcitonin gene-related peptide. In response to 150 and 600 pmol · min^{-1} infusion rates, atrial natriuretic factor concentrations decreased in both the coronary sinus and peripheral artery. At the highest calcitonin gene-related peptide infusion rate, atrial natriuretic factor concentrations in the peripheral artery and coronary sinus were 436 ± 115 pg · ml^{-1} ($p < 0.01$) and 1678 ± 357 pg · ml^{-1} ($p < 0.01$), respectively.

CATECHOLAMINE CONCENTRATIONS: At baseline, plasma norepinephrine and epinephrine concentrations were 1.294 ± 0.415 and 0.150 ± 0.118 ng · ml^{-1}, respectively. In response to the 600 pmol · min^{-1} calcitonin gene-related peptide infusion rate, plasma norepinephrine and epinephrine concentrations increased to 1.818 ± 0.536 and 0.433 ± 0.049 ng · ml^{-1}, respectively ($p < 0.05$).

DISCUSSION

The major emphasis of this study is that calcitonin gene-related peptide does not directly affect the left ventricular myocardial contractility of failing hearts. An increase in coronary blood flow associated with an increase in coronary sinus oxygen saturation was observed only in response to the 2 highest doses of the peptide, whereas myocardial oxygen consumption remained unchanged. These hemodynamic changes were associated with both decreased plasma atrial natriuretic factor concentrations and increased plasma catecholamine concentrations.

Results obtained in experimental animals have suggested that calcitonin gene-related peptide may be involved in the modulation of coronary vasomotor tone and cardiac contractility.[16-21] The possibility that calcitonin gene-related peptide could exert a direct effect on cardiac contractility has been suggested by several studies. A pronounced positive inotropic effect of calcitonin gene-related peptide has been shown in both the spontaneously beating right atrium and the perfused whole heart preparation of guinea pigs and rats.[22-24] This positive inotropic action of calcitonin gene-related peptide on the atrium is thought to be a direct one, because it persists in the presence of adrenergic and histaminergic blocking agents, as well as prostaglandin inhibitors.[21-24] Furthermore, in the atrial membranes of rats, calcitonin gene-related peptide stimulates adenylate cyclase activity, suggesting that cardiac effects of the peptide could be mediated through the formation of cyclic adenosine monophosphate.[25] In human tissues, calcitonin gene-related peptide has been shown to cause a concentration-

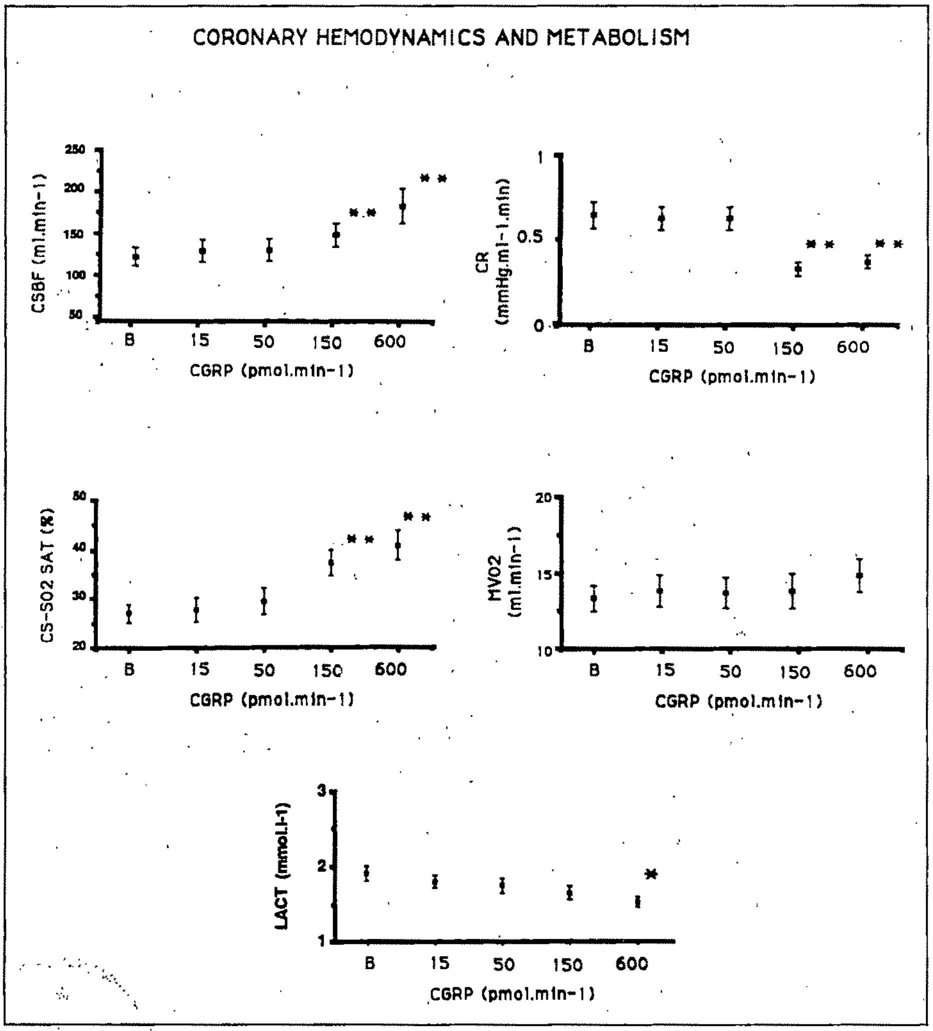

FIGURE 2. Coronary blood flow increased at 2 highest calcitonin gene-related peptide (CGRP) infusion rates, with increase in coronary sinus oxygen saturation (CS-SO2 SAT) and decrease in coronary resistance (CR). B = baseline; CSBF = coronary sinus blood flow; LACT = coronary sinus lactate concentration; MVO2 = myocardial oxygen consumption; *p <0.05; **p <0.01.

dependent positive inotropic effect on pieces of electrically driven, right auricles.[4,23] In contrast with the effects of calcitonin gene-related peptide on the atrium, experiments performed in cultured rabbit and human ventricular myocytes, as well as rat papillary muscles, have not shown an inotropic effect of calcitonin gene-related peptide.[4,10] In human studies, the intravenous administration of calcitonin gene-related peptide in normal subjects and patients with congestive heart failure has been shown to exert positive inotropic actions estimated from measurements of noninvasive cardiac functional indexes.[4,8,10-12] However, such effects that occur concomitantly to the development of hypotension and tachycardia may result from reflex sympathetic activation with increased catecholamine release or other indirect effects of calcitonin gene-related peptide.[7,8] The positive inotropic effect of the peptide in normal subjects has also been shown to be abolished by β blockade.[8] In the present study, left ventricular dP/dt remained unchanged at the 2 lowest doses of the peptide, which suggests that it does not directly affect cardiac contractility at low doses. The highest doses of the peptide cause (as previously reported in other studies) hypotension, decreased cardiac filling pressures and increased heart rate and plasma catecholamine concentrations. All these alterations may have influenced peak positive left ventricular dP/dt explaining the slight but nonsignificant increase in left ventricular dP/dt. This suggests that the intrinsic myocardial contractility of failing hearts is not mainly affected by the peptide administration. Furthermore, preserved contractile responsiveness of the heart was demonstrated in these patients by the infusion of dobutamine in the left main coronary artery. These findings suggest that the primary beneficial cardiovascular effect of calcitonin gene-related peptide in patients with congestive heart failure is a vasodilating action on resistive peripheral vascular beds rather than a direct action on left ventricular myocardial contractility.

In the present study, the 2 lowest infusion rates did not affect coronary blood flow. Recently McEwan et al[9] reported that similar low infusion rates induce angiographic dilation of epicardial coronary arteries. However, because coronary blood flow is mainly related to the vasomotor tone of small resistive vessels rather than that of large epicardial conducting arteries, it is possible that the peptide has distinct effects at different sites of the coronary vascular bed. The data are also consistent with those of Ludman et al[26] who showed the absence of action of low doses of calcitonin gene-related peptide on coronary resistance vessels at rest in nonischemic myocardium. Only the 2 highest doses of calcitonin gene-related peptide increased coronary blood flow. It should be emphasized that on a molar basis, similar potencies of calcitonin gene-related peptide have been shown to increase coronary blood flow in pigs and rabbits, as well as forearm blood flow in humans.[20,22,27] However, simultaneous with changes in coronary hemodynamics, systemic vasodilation occurred in response to the 2 highest calcitonin gene-related peptide doses associated with an increase in cardiac output and a decrease in both systemic arterial and cardiac filling pressures. Therefore, it is possible that an increase in cardiac output and changes in the loading conditions of the heart may have contributed to increase coronary blood flow.[28] However, it is unlikely that the increase in coronary blood flow reflected an adaptative response to an enhanced myocardial metabolic demand, because myocardial consumption did not change and oxygen content in the coronary sinus blood flow increased. This is consistent with a coronary vasodilatory action of the peptide at high doses.

It was previously suggested that vascular calcitonin gene-related peptide effects may be due to an indirect action of the peptide and potentially to an increase in atrial natriuretic factor release.[29] Because plasma atrial natriuretic factor concentrations did not change in the coronary sinus at the 2 lowest doses, it is unlikely that atrial natriuretic factor release is affected by calcitonin gene-related peptide infusion. Since the 2 highest doses of calcitonin gene-related peptide were associated with a decrease in cardiac filling pressures, this suggests that the decrease in plasma atrial natriuretic factor concentrations reflects an improvement in cardiac function. These observations do not support a direct action of calcitonin gene-related peptide on atrial natriuretic factor release.

The physiologic importance of calcitonin gene-related peptide in patients with heart failure remains unclear. In the present study, the effects of calcitonin

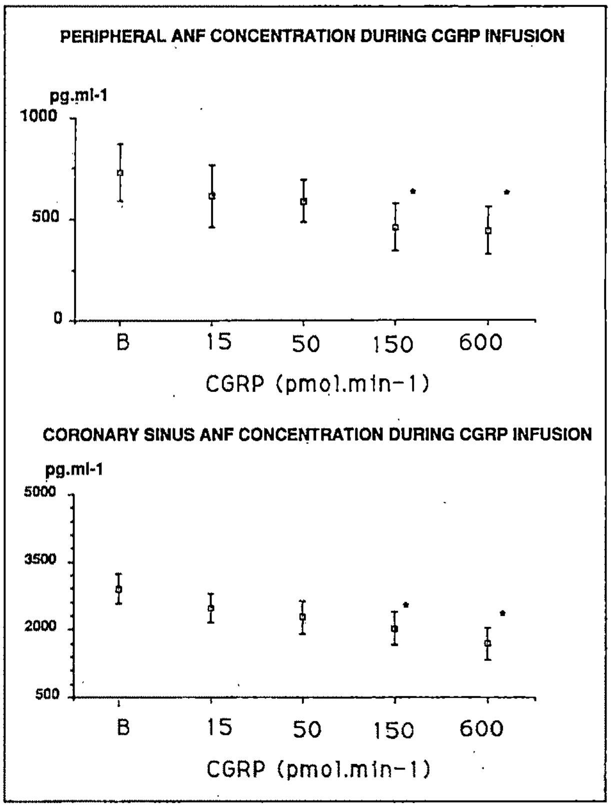

FIGURE 3. Plasma concentrations of atrial natriuretic factor (ANF) decreased in both coronary sinus and femoral artery at 2 highest calcitonin gene-related peptide (CGRP) infusion rates. *p <0.05.

gene-related peptide occurred only at high doses, which presumably increased the concentrations of circulating calcitonin gene-related peptide to higher levels than the physiologic range. However, because infusion studies do not simulate the local release of the peptide, it is therefore possible that the pharmacologic effect of the infusion of calcitonin gene-related peptide may not reflect the physiologic action of this peptide. Therefore, further studies are needed to explore the physiologic role of sensory neuropeptides.

A potential beneficial action of calcitonin gene-related peptide in the treatment of patients with heart failure has been previously suggested.[10,12] However, its potent vasodilating action, inducing hypotension and reflex-sympathetic stimulation found in most clinical studies, may limit its use as a therapeutic agent.

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Influence of Left Ventricular Hypertrophy and Function on the Occurrence of Ventricular Tachycardia in Hypertrophic Cardiomyopathy

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Celia M. Oakley, MD, and Petros Nihoyannopoulos, MD

Sixty-nine patients with hypertrophic cardiomyopathy were studied by 2-dimensional and Doppler echocardiography and 72-hour Holter monitoring to examine the relation between the degree of left ventricular (LV) hypertrophy and dysfunction and the occurrence of ventricular tachycardia (VT). Episodes of nonsustained VT were detected in 20 patients (29%). Maximal wall thickness was not different between patients with (22 ± 5 mm) and without (21 ± 5 mm) VT. Total hypertrophy score, calculated as the sum of 10 segmental wall thicknesses, was also similar in both groups (157 ± 22 and 153 ± 32 mm, respectively; p = not significant). Furthermore, no significant differences were found between the 2 groups in LV end-diastolic dimension (41 ± 7 vs 40 ± 6 mm), fractional shortening (33 ± 7 vs 34 ± 10%) and left atrial size (40 ± 10 vs 41 ± 11 mm). An LV outflow tract gradient was detected in 25% of patients with and 35% without VT (p = not significant). One or more Doppler indexes of diastolic function were abnormal in 70% of patients, but no difference in any of these indexes was found between those with and without VT. In summary, the occurrence of VT in hypertrophic cardiomyopathy is not related to the degree of LV hypertrophy, outflow tract gradient or dysfunction. This finding suggests a dissociation between the arrhythmogenic substrate and echocardiographic features of the disease.

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The association between left ventricular (LV) hypertrophy and the occurrence of ventricular arrhythmias remains controversial. Some investigators[1-3] described a high incidence of ventricular arrhythmias in hypertensive LV hypertrophy, whereas others did not reproduce this finding.[4,5] In hypertrophic cardiomyopathy (HC), a number of previous studies[6,7] (but not all)[8,9] demonstrated an association between the degree of LV hypertrophy and the occurrence of ventricular tachycardia (VT).

Despite its importance, the mechanism of ventricular arrhythmia in HC has not been elucidated and the relation between the arrhythmic substrate and other characteristic features of the disease such as LV hypertrophy, diastolic dysfunction and outflow tract gradient remains uncertain. This study examines the relation between the extent of LV hypertrophy, LV dysfunction and the occurrence of VT during prolonged ambulatory electrocardiographic monitoring.

METHODS

Patients: Between 1989 and 1991, 69 consecutive patients (44% male, mean age 45 years, range 16 to 77) with a documented diagnosis of HC were studied. The diagnosis of HC was established by 2-dimensional echocardiography, and in all patients, a nondilated, hypertrophied left ventricle was demonstrated in the absence of any systemic or cardiac disease that could produce such LV hypertrophy.[10] Thirty patients (43%) were in New York Heart Association functional class I, 22 (32%) in class II, and 17 (25%) in class III. The pattern of LV hypertrophy was asymmetric in 59 patients (86%), concentric in 9 (13%), and distal in 1 (1%). All cardioactive medications were discontinued before the study in most patients (91%). However, in 3 patients (2 on β-blockers, and 1 on a calcium antagonist), medication was not withdrawn owing to severe symptoms. In the only 3 patients who were receiving long-term amiodarone therapy, the drug was not discontinued owing to previous cardiac arrest or documented, symptomatic episodes of VT.

Holter monitoring: Holter monitoring was performed using "Tracker" recorders (Reynolds Medical). A 2-channel recording was obtained with electrodes positioned according to the maximal R voltage on the 12-lead electrocardiogram. Tapes were analyzed by a technician on a Pathfinder 3 high-speed analyzer (Reynolds Medical) and reviewed by 1 investigator. Maximal and minimal heart rates, the number of supraventricular and ventricular extrasystoles per 24 hours, and the occurrence of supraventricular tachycardia or VT were re-

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TABLE I Demographic Data and Clinical Variables

	VT (n = 20)	Non-VT (n = 49)	p Value
Age (year) (range)	48 ± 15 (16–71)	42 ± 16 (16–77)	NS
Sex (women/men)	13/7	26/23	NS
NYHA class			
I	8 (40%)	22 (45%)	NS
II	7 (35%)	15 (31%)	
III	5 (25%)	12 (25%)	
Symptoms			
Syncope	11 (55%)	14 (29%)	<0.05
Chest pain	13 (65%)	30 (61%)	NS

NS = not significant; NYHA = New York Heart Association; VT = ventricular tachycardia.

corded. Nonsustained VT was defined as >3 extrasystoles at a rate of >120 beats/min terminating spontaneously.

Two-dimensional echocardiography: A complete echocardiographic study was performed in each subject[11] using a Toshiba SSH 160A ultrasound system, with a 3.75 MHz transducer for cardiac imaging and a 2.5 MHz for Doppler. All measurements were obtained using recorded images on a ¾-inch videotape recorder. LV diastolic and systolic dimensions were obtained from the short-axis parasternal view, and fractional shortening (%) was subsequently calculated. The extent of LV hypertrophy was estimated from serial short-axis views at 3 different levels (mitral, papillary muscles, and apex). At the mitral and papillary levels, the ventricle was divided in 4 equal-sized regions that identified the anterior and posterior septum, and the inferior and lateral walls. At the apical level, the ventricle was divided in 2 regions identified as the anterior septum and inferior wall. Wall thickness was measured in each region by identification of the endocardial and epicardial borders. Maximal wall thickness was identified, and a total hypertrophy score was calculated as the sum of all 10 measurements of segmental thickness (Figure 1).

Doppler examination: LV outflow tract velocities were recorded from the apical 5-chamber view by pulse wave and when velocities were high (>1 m/s) by continuous-wave Doppler. Peak outflow tract gradient was estimated from the simplified Bernoulli's equation (peak gradient = $4 \times$ maximal velocity^2). Diastolic filling was assessed by recording the transmitral flow velocity profile after the sample volume was positioned in the LV inflow at the level of the mitral leaflet tips. The following Doppler indexes were obtained: 1) peak early flow velocity (E), in m/s; (2) peak late flow velocity (A), in m/s; (3) E/A ratio; (4) isovolumic relaxation time measured from the Doppler artefact of aortic valve closure to the onset of transmitral diastolic flow, in ms; (5) duration of early diastolic flow, in ms; and (6) mean deceleration rate of early diastolic flow, in m/s^2. Three cardiac cycles were used to obtain an average value for each Doppler parameter. All 2-dimensional and Doppler echocardiographic measurements were obtained by the same observer who had no knowledge of the Holter monitoring findings, in order to eliminate bias.

Statistical analysis: Continuous variables were compared using Student's *t* test. Proportions were compared using chi-square test. Data are expressed as mean ± SD. A p value <0.05 was considered statistically significant.

RESULTS

Holter monitoring: Episodes of nonsustained VT were identified in 17 patients (25%). Six patients had an average of 1 episode of VT/24 hours, 1 patient had >25 episodes, and the remaining 10 patients had an average of 4 episodes/24 hours. Five patients had prolonged runs of >7 beats and 12 patients had short runs of 4 to 7 beats. No patient with VT was receiving amiodarone, but 1 was receiving propranolol. An additional 3 patients, all receiving amiodarone and without evidence of VT, were included in the VT group; 1 was rescuscitated from out-of-hospital cardiac arrest due to documented ventricular fibrillation, and the other 2 had repeatedly shown symptomatic VT in the past (before 1989) on Holter monitoring. The basic rhythm was sinus in 17 patients, atrial fibrillation in 2, and paced (VVI) in 1. The remaining 49 patients had no VT during monitor-

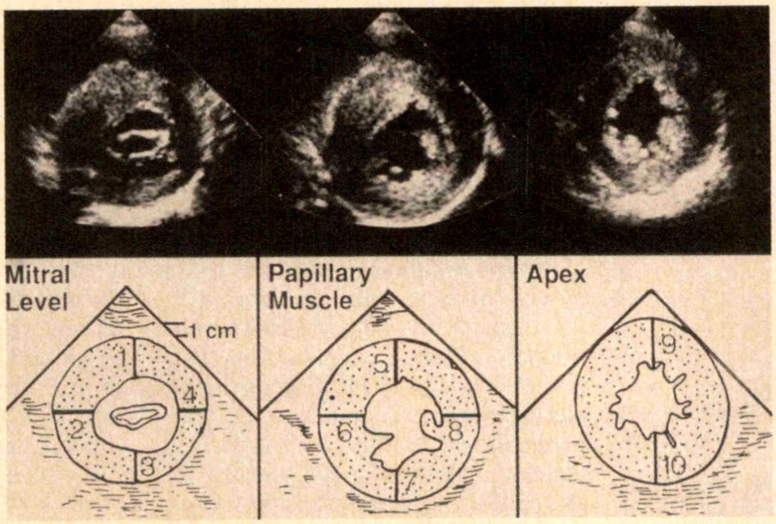

FIGURE 1. Two-dimensional echocardiographic measurement of extent of left ventricular hypertrophy. Short-axis views were obtained at 3 levels (as shown). Wall thickness was measured in 10 segments (1 to 10): 1, 5 and 9 = anterior septum; 2 and 6 = posterior septum; 3, 7 and 10 = inferior wall; and 4 and 8 = lateral wall. Total hypertrophy score was calculated as sum of all 10 measurements.

ing and no evidence of VT in the past; none was receiving amiodarone, but 1 was receiving a β blocker and 1 a calcium antagonist. The basic rhythm in this group was sinus in 45 patients and atrial fibrillation in 4. The clinical features of the VT and non-VT groups are listed in Table I.

Frequent ventricular extrasystoles (>30/hour) were identified in 9 patients (45%) with VT compared with 2 (4%) without VT ($p < 0.001$). History of syncope was more frequent among patients with VT (Table I). During follow-up (median 1.1 years, range 3 months to 2.2 years), 1 sudden death occurred in a patient without VT, and 1 out-of-hospital cardiac arrest occurred in a patient with frequent VT. Neither patient was receiving drug treatment. Family history of sudden death (first-degree relative) was present in 3 patients (15%) with VT compared with 8 (16%) without VT (p = not significant [NS]).

Two-dimensional echocardiography (Table II): The degree of LV hypertrophy (expressed by either maximal wall thickness or total hypertrophy score) was not different between patients with and without VT. Maximal wall thickness ranges were 13 to 32 mm in the group with VT and 13 to 35 mm in the group without VT. The corresponding total hypertrophy score ranges for the 2 groups were 126 to 227 and 107 to 246 mm, respectively. The numbers of hypertrophied segments at all levels and regions were also similar between the 2 groups (4.4 ± 2.3 vs 4.0 ± 2.3 for VT and non-VT group, respectively; p = NS). LV diastolic and systolic dimensions, left atrial size and fractional shortening did not differ between the groups. The degree of LV hypertrophy was also not different between patients with or without history of syncope.

Doppler echocardiography (Table III): One or more abnormal indexes of diastolic function were detected in 48 patients (70%) with HC compared with normal subjects at our institution.[12] No significant differences were found between patients with and without VT in either the outflow velocity profile or the indexes of diastolic function. An outflow tract gradient (>30 mm Hg) was present in 5 patients (25%) with VT compared with 17 (35%) without VT (p = NS). An A wave and E/A ratio were obtained from patients in sinus rhythm (17 with and 45 without VT). The E/A ratio was <1 in 10 patients (59%) with VT and 22 (49%) without VT (p = NS). Isovolumic relaxation time was measured in 64 patients (18 with and 46 without VT) and was prolonged (>90 ms) in 12 patients (67%) with and 27 (59%) without VT (p = NS). Neither the degree of outflow gradient nor any Doppler index of diastolic function was different between patients with and without history of syncope.

DISCUSSION

Left ventricular hypertrophy: In this consecutive HC cohort, 20 patients (29%) had electrocardiographic or clinical evidence of VT during 72-hour Holter monitoring, an incidence similar to that of previous reports.[6-9] In agreement with previous studies,[8,9] we found no relation between the extent of LV hypertrophy and the occurrence of ventricular arrhythmias. However, this absence of correlation was in disagreement with other studies[6,7] that found a relation between the magnitude of LV hypertrophy and the presence of high-grade arrhythmias. Those studies used only M-mode measurements of ventricular septal thickness or limited 2-dimensional echocardiography. In the present study, we used extensive 2-dimensional assessment of the degree of LV hypertrophy by estimating total ventricular hypertrophy from the sum of 10 segments at mitral, papillary muscle level and apex. The previously reported[7] correlation between the extent of LV hypertrophy and the occurrence of VT may be explained by selection of patients on the basis of severe hypertrophy and a difference in age between the groups with and without VT.

TABLE II Two-Dimensional Echocardiographic Results

	VT (n = 20)	Non-VT (n = 49)	p Value
LV diastolic diameter (mm)	41 ± 7	40 ± 6	NS
LV systolic diameter (mm)	28 ± 7	27 ± 7	NS
Left atrial diameter (mm)	40 ± 10	41 ± 11	NS
Fractional shortening (%)	33 ± 7	34 ± 10	NS
Maximal wall thickness (mm)	22 ± 5	21 ± 5	NS
Hypertrophy score (mm)	157 ± 22	153 ± 32	NS
Type of hypertrophy			
Asymmetric	17 (85%)	42 (86%)	NS
Concentric	3 (15%)	6 (12%)	
Distal	—	1 (2%)	

LV = left ventricular; NS = not significant; VT = ventricular tachycardia.

TABLE III Doppler Echocardiographic Results

	VT (n)	Non-VT (n)	p Value
RR interval (ms)	917 ± 160 (20)	872 ± 153 (49)	NS
LV outflow tract velocity (m/s)	2.0 ± 0.7 (20)	2.4 ± 1.2 (49)	NS
Early/late transmitral flow velocity ratio	0.9 ± 0.5 (17)	1.2 ± 0.7 (45)	NS
Isovolumic relaxation (ms)	94 ± 20 (18)	92 ± 21 (46)	NS
Deceleration of early diastolic flow (m/s^2)	2.8 ± 1.5 (20)	3.1 ± 1.3 (49)	NS
Duration of early diastolic flow (ms)	250 ± 61 (20)	238 ± 56 (49)	NS

Abbreviations as in Tables I and II.

Left ventricular function: In this study, 2-dimensional echocardiography showed no difference in LV dimensions, fractional shortening and presence of intraventricular gradient between patients with and without VT. Typically in HC, isovolumic relaxation is prolonged, filling is slow, and the proportion of filling resulting from the atrial contraction may be increased. These changes are reflected in the Doppler recordings of transmitral diastolic flow.[13-15] Although patients in this study had similar diastolic abnormalities as a whole, there were no differences in any Doppler indexes of diastolic function between those with and without VT. This is in agreement with the findings of Fananapazir et al[16] who showed no difference between HC patients with and without VT on Holter monitoring in either the magnitude of outflow obstruction assessed by catheterization or ejection fraction and peak diastolic filling assessed by radionuclide angiography.

Mechanisms of ventricular tachycardia in hypertrophic cardiomyopathy: The mechanism of VT in HC remains uncertain, but evidence in favor of a reentry mechanism comes from both the results of electrophysiologic studies[17-20] that confirmed reproducible induction of VT and the higher frequency of late potentials detected by signal-averaging electrocardiography in patients with HC compared with control subjects.[21] It is possible that myocardial disarray (a characteristic finding in HC)[22] rather than ventricular hypertrophy itself can cause spatial dispersion of the electrical impulse to provide the background for a reentry circuit. Pathologic fibrosis and matrix connective tissue (which have been detected in the myocardium of patients with HC)[23] may also contribute to providing an abnormal electrophysiological background. The dissociation between the arrhythmogenic substrate in HC and other morphologic features of the disease is supported by reports of families where an electrical abnormality or myocardial disarray was present without increase in wall thickness.[24-26] Myocardial ischemia (occasionally detected in HC patients)[27] could also have a role in the occurrence of VT. Similarly, abnormalities of adrenergic tone[28] may constitute a potential mechanism of ventricular arrhythmia in HC.

Study limitations: An important limitation of this study may be the absence of intracardiac electrophysiologic studies. It has been suggested that electrophysiologic studies are more sensitive than is Holter monitoring in detecting ventricular electrical instability[18] and also identifying potential mechanisms for cardiac arrest in most patients with HC.[20] However, interpretation of aggressive stimulation protocols that can induce short episodes of polymorphic VT (a nonspecific response in other clinical settings) remains uncertain. Furthermore, there is no established stimulation protocol that has been used in a wide range of cardiac pathologies and proved to be specific in detecting electrical instability in HC.

During the present study, a small number of patients was receiving cardioactive medication that could not be discontinued owing to severe symptomatology. However, the effects of these drugs on LV hypertrophy are not thought to be significant. Although we found an association between history of syncope and VT, follow-up in our patients was too short to determine whether VT had the same increased risk of sudden death as reported in earlier studies.[29] Finally, the present study was of an adult cohort, and the results cannot be extrapolated to children with HC, because spontaneous arrhythmias are infrequent in children and adolescents with HC, despite the higher mortality in this group than in adults.[30]

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Front-Loading of Double-Umbrella Devices, a New Technique for Umbrella Delivery for Closing Cardiovascular Defects

Stanton B. Perry, MD, and James E. Lock, MD

In all, 22 defects (6 atrial septal, 13 ventricular septal, 2 patent ductus arteriosus and 1 coronary artery fistula) in 17 patients were closed with double umbrellas using a new delivery technique, front-loading. The umbrella was loaded in the sheath outside the body and then advanced without use of the rigid pod to the defect. The defect was successfully closed in all 17 patients, including 5 in whom standard delivery techniques were unsuccessful. Front-loading enables the double umbrella to be delivered through a smaller long sheath than does the standard technique, and enables the flexible umbrella rather than the rigid pod to be advanced through curves in the sheath, and may improve delivery of double-umbrella devices to inaccessible parts of the circulation.

(Am J Cardiol 1992;70:917–920)

Double-umbrella vascular occluding devices (Bard PDA Umbrella, Bard Clamshell Septal Umbrella, USCI Division, C.R. Bard, Billerica, Massachusetts) are being placed and have proved useful in a growing list of intravascular locations. In addition to placement in patent ductus arteriosus[1] and atrial septal defects,[2] these devices have been used to close venous anomalies,[3] coronary arteriovenous fistulae, congenital[4] and postinfarction ventricular septal defects,[5] pulmonary arteriovenous fistulae,[6] valvular and paravalvular leaks, baffle fenestrations after the Fontan operation,[7] and surgical aortopulmonary shunts.[3]

The current delivery system comprises 3 co-axial units. The innermost wire controls locking and releasing of the umbrella. Surrounding this wire is a second one that provides support for the control wire and through which the control wire slides. The proximal 30 cm of the outer wire is a hollow rod, and the distal 87 cm are wound and flexible. Surrounding this double wire is an 85 cm woven catheter through which the wires slide. At the distal end of this outer catheter is the metal pod in which the umbrella is folded for delivery. The pod ranges between 12 and 40 mm in length depending on the size of the umbrella. The pod (the part of the system with the largest diameter) determines the size of the long sheath used for delivery (8Fr for 12 mm umbrellas and 11Fr for larger ones).

As originally conceived, the umbrella would be delivered and opened in the defect directly from the pod. In practice, this did not work for 2 reasons. First, the delivery system was too inflexible to enable it to be maneuvered across the defect. Second, the straight metal pod would not follow curves in a long sheath placed across the defect. For these reasons, Mullins et al[1] developed the technique that is currently used for umbrella delivery. A long sheath is positioned across the defect to be closed. The double umbrella is loaded in the metal pod outside the body, and the delivery system is advanced through the sheath to the junction of the inferior vena cava and right atrium. Using the double wire, the umbrella is advanced out of the pod and through the sheath until it is positioned across the defect. The pod is left in the inferior vena cava, and the umbrella is opened using the interaction between the double wire and sheath.

Front-loading the umbrella from the pod into the sheath outside the body instead of in the inferior vena cava has several advantages. First, because the metal pod determines the size of the sheath needed, a smaller sheath can be used for delivery. Second, as the pod will not follow curves through the heart, it will occasionally not follow curves through the femoral and iliac vessels.

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TABLE I Patients

Pt. No.	Age (year)	Weight (kg)	Defect Closed	Umbrella Size (mm)	Sheath (Fr)
1	0.25	4.2	Atrial septal defect	17	10
2	0.8	11.5	Atrial septal defect	23	10
3	1.2	7.9	Atrial septal defect	17	10
4	1.3	11	Atrial septal defect	23	10
5	1.7	8.5	Atrial septal defect	23	10
6	77	63	Patent foramen ovale	33	11
7	0.4	4.2	Apical VSD	12	7
8	0.8	6.8	Midmuscular VSD	23	10
9	1	6	Anterior & apical VSDs	12,23	7,10
10	1.1	5.8	Apical VSD	23	10
11	1.3	7.4	3 anterior VSDs	17,17,28	10
12	1.3	9	Anterior & posterior VSDs	17,23	10
13	1.4	7	Apical VSD	17	11
14	6.5	19	Anterior & apical VSDs	12,17	7,10
15	1.25	11	Coronary fistula	12	7
16	17	51	Patent ductus arteriosus	12	7
17	1.1	9	Patent ductus arteriosus	12	7

VSD = muscular ventricular septal defect.

Finally, eliminating the outer catheter simplifies the system. Currently, there are 3 parts that can move independently during delivery: the wire, catheter and sheath. Eliminating the catheter removes 1 moving part. For this approach to be effective, the umbrella must track easily for long distances through a sheath ≥1Fr size smaller than is currently used, the sheath must retain its shape and characteristics without the stiffening influence of the pod and delivery catheter, and the umbrella release mechanism must remain unimpaired.

Between September 1989 and March 1992, we encountered several clinical cases in which standard umbrella techniques were not capable of closing the defects. In infants, the vein or artery may be too small to accept standard-sized long sheaths. Tortuous catheter courses are more easily traversed by the flexible umbrella than the metal pod in which the umbrella is folded. Some defects may be too small to be crossed with standard-sized sheaths without prior dilation. In each case, front-loading the umbrella in the sheath outside the body enabled successful closure of the cardiac defect.

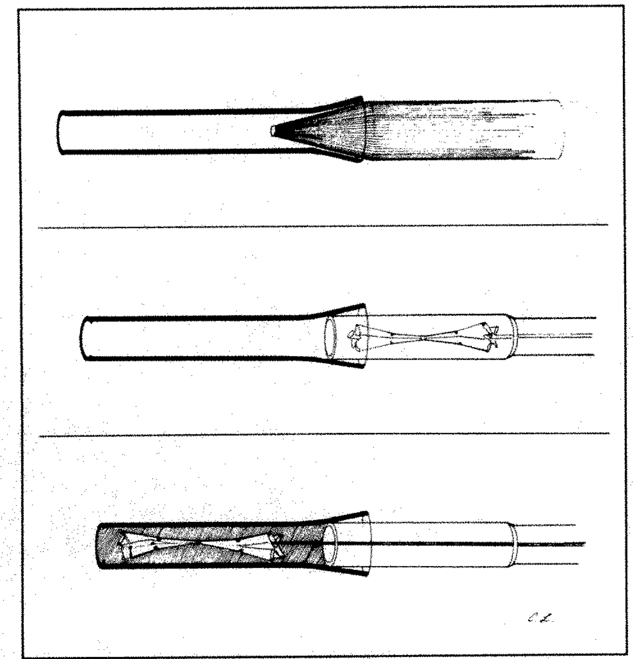

FIGURE 1. Cut end of sheath is flared, using oversized dilator *(top)*. Pod with loaded umbrella is inserted in flared end of sheath *(middle)*. Umbrella is then advanced out of pod and into sheath *(bottom)*.

METHODS

Patients: Since September 1989, 22 defects in 17 patients have been closed with double umbrellas using the front-loading technique. An atrial septal defect was closed in 6 patients, 13 muscular ventricular septal defects in 8 patients, 1 patent ductus arteriosus in 2 patients and 1 coronary artery fistula in 1 patient (Table I). In all 17 patients, selection for placement of the double-umbrella device, and selection of device size and technique (other than front-loading) followed processes previously described.[1-7]

Technique for front-loading: In each of 17 patients, the umbrella was loaded in the pod of the delivery catheter, as previously described.[1] A long sheath was positioned across the defect. One operator held the distal end of the metal pod carefully and firmly within the end of the long sheath, and another advanced the wire, pushing the umbrella out of the pod and into the sheath. If a sheath smaller than the standard was used, it was necessary to cut the proximal end of the sheath or remove its coupling device and flare this end by pressing an oversized dilator (e.g., 9Fr for 7Fr long sheath) into the cut end. This was performed to enable the pod to fit in the proximal end of the sheath, so that the umbrella could be advanced smoothly in the sheath (Figure 1).

Since the current delivery catheter was not designed for front-loading, the excess amount of wire available to advance the umbrella out of the pod is only approximately 17 to 20 cm. Because the proximal end of the sheath was >17 cm from the defect, it was necessary to remove (by scalpel) a 30 to 60 cm section of the wall of

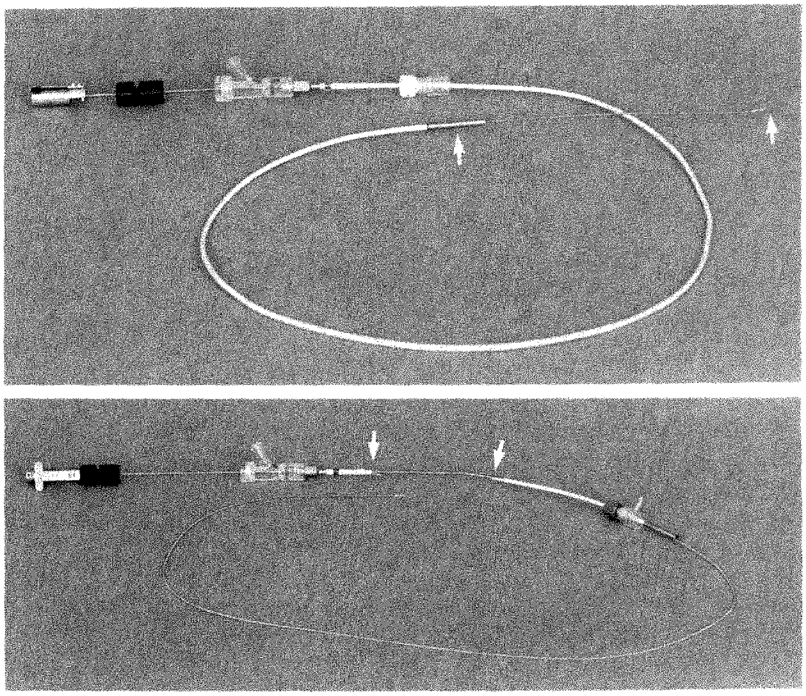

FIGURE 2. Intact delivery system *(top)* is shown with central wire *(between arrows)* extending out from pod at end of catheter. After cutting and removing most of catheter *(arrows point to cut ends)*, much longer segment of central wire is exposed *(bottom)*.

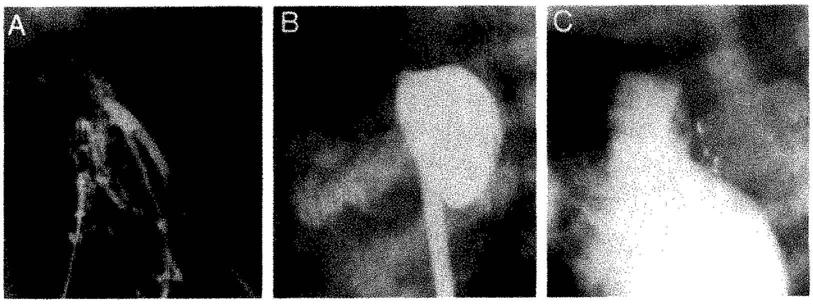

FIGURE 3. Injection in left femoral vein *(A)* demonstrates complete obstruction of vessel by sheath at iliac bifurcation, and umbrella is seen in sheath. Left atrial injection *(B)* through sheath demonstrates atrial septal defect. Right atrial injection *(C)* after umbrella release demonstrates that umbrella is well-positioned.

the catheter, which surrounds the double wire (Figure 2). To avoid kinking or otherwise damaging the outer support wire and its inner release mechanism, it is best to slice the catheter in sections, using the proximal portion of the wire (which is a solid metal tube) as a support.

After an adequate amount of wire was exposed, the umbrella was advanced through the long sheath to the level of the defect. At that stage, the distal arms were opened, the entire apparatus was withdrawn to the level of the defect, and the sheath was withdrawn to enable the proximal arms to open. Correctly positioned devices were released as described, and angiography and echocardiography were used to assess the adequacy of positioning and closures.

Informed consent: Clinical use of these umbrellas was performed under the auspices of an experimental protocol approved by the Food and Drug Administration, and the committee on clinical investigation at The Children's Hospital. Umbrellas were placed in ventricular septal defects only after consultation with the patient's primary cardiologist and cardiac surgeon. Informed consent was obtained from the patient or the patient's parents in each case.

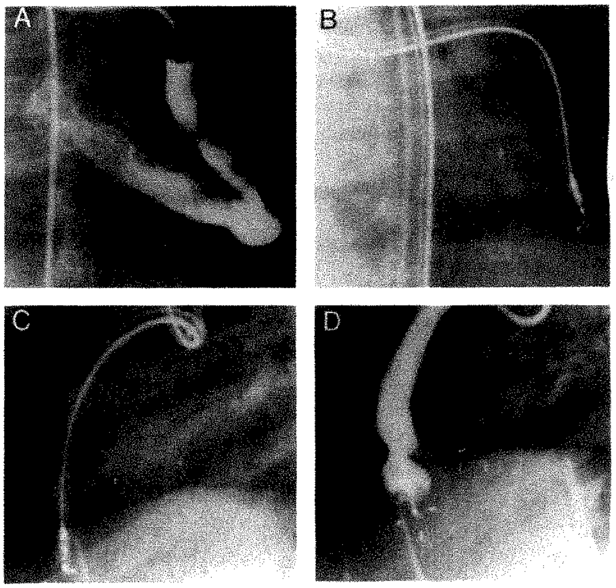

FIGURE 4. Injections in left anterior descending coronary artery show fistula before *(A)* and after *(D)* umbrella closure. Anteroposterior *(B)* and lateral *(C)* projections show tortuous course of sheath in aorta and coronary artery after delivery of distal arms of umbrella.

RESULTS

Catheter manipulation to defect: In 7 of 17 patients, an attempt was made to use standard delivery techniques. In 6 of these cases, the standard delivery sheath could not be correctly positioned owing to size limitations of the vessel used for access (patient 1; Figure 3) or of the defect (patient 16), or to the inability to negotiate curves in the catheter course (patients 7, 8, 10 and 13). In patient 6, in whom an 11Fr sheath reached the defect, the rigid pod would not follow the curves along the sheath in the tortuous iliac veins. In the remaining 10 patients, front-loading was performed without previously attempting standard techniques. In patients 15 and 17, a retrograde femoral artery approach was used to close a coronary artery fistula (Figure 4) and a patent ductus arteriosus, respectively, and front-loading with a smaller sheath was used to minimize arterial injury.

Delivery of umbrella: In all cases, umbrellas were able to negotiate the twists and kinks in the long sheath, even when the pod could not be advanced across these kinks. The process of getting the collapsed umbrella to negotiate difficult curves was facilitated by applying firm advancing pressure, straightening the sheath as much as possible or advancing the sheath and umbrella as 1 unit when a kink had become severe.

Complications: Of 17 patients, 7 needed a blood transfusion. Using conventional delivery techniques, blood loss is minimized owing to the fit between the pod and sheath. Because the pod is not delivered into the sheath with the front-loading technique, achieving hemostasis becomes a problem. Initially, hemostats were applied to the outside of the sheath or knotted rubber bands were placed at the end of the sheath to achieve hemostasis. However, 3 of the first 6 patients (including both with ventricular septal defects) needed transfusion. Subsequently, hemostasis was achieved by holding the pod in the flared end of the sheath or constructing sidearm adaptors from appropriately sized sheaths with backstops. Using these techniques, 4 of the last 11 patients needed transfusion, 3 of whom had multiple ventricular septal defects closed.

There were no strokes, cardiac or vascular damage, or intractable difficulties with device placement.

DISCUSSION

Front-loading of vascular occlusive devices in delivery catheters outside the body is not a new technique; Gianturco coils come loaded in a rigid cylinder and are extruded directly in the delivery catheter outside of the body.[8] A similar approach for double-umbrella devices has several advantages; it would allow a reduction of ≥1Fr in the size of the delivery catheter, make umbrella traversal of vascular kinks easier and increase the number of lesions that could be reached by the occlusive umbrellas.

The initial clinical applications of this technique, although crude, were relatively successful; we closed atrial and ventricular septal defects in patients weighing as little as 4.2 kg, and closed defects in 5 patients in whom standard techniques were unsuccessful. There were no problems with vascular access or deployment of the devices owing to use of the front-loading technique, and the umbrellas had no evidence of distortion as a result of passage through the entire length of the long sheath.

Despite these successes, several technical problems were identified that need to be addressed; the entire current delivery system configuration needs to be modified, so that the delivery wire is sufficiently long to obviate the need to excise part of the catheter. The minimal sheath size for each double-umbrella device should be identified in advance (e.g., it may be that a 9Fr sheath would suffice to deliver the Bard Clamshell septal occluder, rather than the current 11Fr size).

Until the delivery system is modified to enable front-loading, flushing and hemostasis can be achieved using sidearm adaptors. If a standard size long sheath is used, the pod can be left in the proximal end of the long sheath and the sidearm adaptor that comes with the delivery system used. When a small long sheath is used, it is necessary to remove the coupling device and flare the end. For these cases, a short sheath with a backstop of standard size (8 or 11Fr) should be placed over the delivery system before loading the umbrella in the long sheath. The short sheath can then be advanced and pressed inside the flared end of the long sheath.

Although this experience was limited, it illustrates an alternative method for device delivery that may help solve infrequent but important clinical vascular problems and demonstrates the potential advantages of front-loading as a routine method for umbrella delivery.

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Cardiomyopathy of Obesity: A Clinicopathologic Evaluation of 43 Obese Patients with Heart Failure

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Right heart hemodynamic and endomyocardial biopsy abnormalities associated with marked obesity were characterized in 43 obese patients who presented with symptoms of congestive heart failure. Marked obesity was defined as a body mass index $\geq$35 kg/m^2. They were compared to a group of 409 patients with similar presentations but normal body mass. Analysis of the 519 patients showed that body mass index was positively correlated with right heart pressures and cardiac output ($p \leq 0.0001$), pulmonary vascular resistance index ($p \leq 0.003$) and systolic blood pressure ($p \leq 0.0006$). Obese patients had elevated right heart pressures, cardiac output ($p \leq 0.0001$) and pulmonary vascular resistance index ($p \leq 0.02$) when compared with a group of lean patients with a similar degree of cardiomyopathy. After evaluation, a significantly higher percentage of obese patients were found to have idiopathic dilated cardiomyopathy compared with lean patients. A specific etiology was found in 264 (64.5%) of the 409 lean patients compared with 10 (23.3%) of the obese patients ($p \leq 0.0001$). The most common finding on endomyocardial biopsy in the obese group was mild myocyte hypertrophy (67%). These data suggest that the cardiomyopathy of obesity exists and may play an important role in a population referred for the evaluation of heart failure.

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Moderate obesity was once considered to be a sign of good health. We now understand that obesity not only increases morbidity and mortality, but is also a significant predictor of coronary artery disease, coronary death and congestive heart failure independent of other standard risk factors for ischemic cardiac disease.[1-3] Obesity is also associated with an increased incidence of diabetes, hypercholesterolemia and hypertension.[4] Left ventricular dysfunction occurs, and can be associated with pulmonary congestion.[5] Smith and Willius[6] are credited with the first report of the association between obesity and congestive heart failure. Many now consider obesity to be a cause of dilated cardiomyopathy.[7] Despite this, the evaluation of the obese patient with heart failure has not been described. We report our experience with 43 markedly obese patients referred for the evaluation of heart failure. The purpose of this investigation was to characterize the hemodynamic and endomyocardial biopsy abnormalities associated with marked obesity compared with a group of patients with a similar degree of cardiomyopathy but normal body mass.

METHODS

Study subjects: From June 1983 to December 1990, 610 consecutive patients underwent endomyocardial biopsy at The Johns Hopkins Hospital as part of an evaluation for cardiomyopathy. Height and weight data were collected on 519 patients. The 519 patients were stratified into categories using the Quetelet body mass index (kg/m^2), a weight- and height-related index of body fat.[8,9]

Study protocol: Patients were evaluated within 6 months of the onset of congestive heart failure symptoms. All patients underwent a medical history, physical examination, routine blood chemistry and hematologic measurements, and a determination of left ventricular function by echocardiography. Endomyocardial biopsy and right-sided cardiac catheterization were performed through the right internal jugular vein. Standard coronary arteriography was performed in patients who presented with a history of myocardial ischemia, age >35 years, or in the presence of standard cardiovascular risk factors. Coronary arteriography was performed in 21 of the obese patients (49%) and in 158 of the lean patients (38%).

A modified 50 cm Stanford-Caves bioptome was used to collect $\geq$5 specimens from the right intraventricular septum. Specimens were immediately placed in either buffered 10% formalin for light microscopy, 3% glutaraldehyde for electron microscopy, or were fresh-

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TABLE I Hemodynamic Data, Correlation with Body Mass Index

Variable	n = 519	R	p Value
RA mean (mm Hg)	7.0 ± 5.9	0.185	0.0001
RV systolic (mm Hg)	39.9 ± 16.4	0.187	0.0001
RV diastolic (mm Hg)	8.9 ± 6.3	0.220	0.0001
PA systolic (mm Hg)	39.7 ± 16.7	0.192	0.0001
PA diastolic (mm Hg)	17.3 ± 9.7	0.213	0.0001
Wedge (mm Hg)	16.4 ± 9.7	0.177	0.0001
Cardiac output (liters/min)	4.55 ± 1.43	0.316	0.0001
Cardiac index (liters/min/m^2)	2.35 ± 0.65	0.083	NS
Stroke index (ml/beat/m^2)	27.2 ± 9.7	0.060	NS
SVRI (d-s/cm^5/m^3)	3,197 ± 1,097	0.057	NS
PVRI (d-s/cm^5/m^3)	316 ± 277	0.135	0.003
LVSWI (g-m/beat/m^2)	29.3 ± 13.3	0.067	NS
BP systolic (mm Hg)	126 ± 23	0.149	0.0006
BP diastolic (mm Hg)	79 ± 14	0.045	NS
Heart rate (beat/min)	90 ± 19	−0.026	NS
BMI (kg/m^2)	26.3 ± 6.7	1.0	

Values are expressed as mean ± SD.
BMI = body mass index; BP = blood pressure; d-s = diastolic-systolic; LVSWI = left ventricular stroke work index; NS = not significant; PA = pulmonary artery; PVRI = pulmonary vascular resistance index; RA = right atrial; RV = right ventricular; SVRI = systemic vascular resistance index.

TABLE II Body Mass Index

BMI (kg/m^2)	No. of Patients	%
≥50	4	0.8
45–49.9	6	1.2
40–44.9	13	2.5
35–39.9	20	3.9
30–34.9	67	12.9
25–29.9	158	30.4
20–24.9	188	36.2
≤19.9	63	12.1
Total	519	100

Categories by BMI: obese ≥35, lean ≤29.9, excluded 30–34.9.
BMI = body mass index.

frozen for immunoperoxidase stains including common leukocyte antigen (CD45, Hle, Becton-Dickinson, San Jose, California). Right-sided cardiac catheterization was performed in a routine fashion using a fluid-filled, balloon-tipped, flow-directed catheter attached to a quartz transducer. The thermodilution technique, performed in triplicate with <10% variability, was used to determine cardiac output.

Data analysis: Standardized diagnostic criteria were used in this study. A final diagnosis, which included the results of the endomyocardial biopsy, was registered for each patient. The biopsy samples were classified as to the presence or absence of myocarditis or a secondary form of cardiomyopathy. Those with myocarditis were classified according to the "Dallas Criteria." A diagnosis of myocarditis was confirmed by common leukocyte antigen staining.

The following were calculated in the usual fashion: cardiac index (liters/min/m^2), stroke index (ml/beat/m^2), systemic vascular resistance index (d-s/cm^5 /m^2), pulmonary vascular resistance index and left ventricular stroke work index (g-m/beat/m^2).

Statistics: The data are presented as mean ± standard deviation. To test for association between the variables obtained at right heart catheterization and body mass index, the statistical model used was simple linear regression with 1 independent variable, body mass index. Descriptive statistics were generated using 2 body mass index categories. The obese group was defined as having a body mass index ≥ 35 kg/m^2 and the lean group as having a body mass index <30 kg/m^2. Comparisons between these groups were done using a 2-tailed, unpaired *t* test or chi-square test where appropriate. Statistical significance was defined as a probability value ≤ 0.05.

RESULTS

Correlation of body mass index with right heart hemodynamic variables (Table I): The mean age of the 519 study patients was 45 ± 15 years, and 315 (60.7%) were male (Table I). Significant, although weak, positive correlations were found between body mass index and mean right atrial, right ventricular systolic and diastolic, pulmonary artery systolic and diastolic, pulmonary capillary wedge and systolic blood pressures. Similarly, cardiac output and pulmonary vascular resistance index were found to increase as body mass index increased. The strongest association was between body mass index and cardiac output.

Comparison of obese and lean groups (Tables II and III): We classified patients into an obese group, body mass index ≥ 35 kg/m^2, and a lean group, body mass index <30 kg/m^2 (Table II). The majority of the patients in each group were men (obese 65%, lean 61%, p = not significant). The hemodynamic data are presented in Table III. Right heart pressures and pulmonary and systemic vascular resistance indexes were elevated, whereas cardiac, stroke and left ventricular stroke work indexes were decreased in both groups. Heart rate and blood pressure were normal. Obese patients had significantly higher right heart pressures, systolic blood pressure, cardiac output, and pulmonary vascular resistance index than lean patients. There were no differences based on body mass index in heart rate, diastolic blood pressure, systemic vascular resistance index, cardiac index or left ventricular stroke work index.

TABLE III Hemodynamics

Variable	Obese	Lean	P Value
Age (years)	42.2 ± 11.6	45.5 ± 15.4	NS
RA mean (mm Hg)	10.2 ± 6.5	6.4 ± 5.6	0.0001
RV systolic (mm Hg)	47.2 ± 16.7	38.5 ± 16.1	0.0007
RV diastolic (mm Hg)	13.2 ± 7.8	8.2 ± 6.1	0.0002
PA systolic (mm Hg)	47.6 ± 17.3	38.2 ± 16.3	0.0004
PA diastolic (mm Hg)	22.7 ± 11.8	16.2 ± 9.1	0.001
Wedge (mm Hg)	20.8 ± 10.4	15.6 ± 9.5	0.0006
Cardiac output (liters/min)	5.62 ± 1.48	4.41 ± 1.38	0.00001
Cardiac index (liters/min/m^2)	2.33 ± 0.55	2.40 ± 0.66	NS
Stroke index (ml/beat/m^2)	24.5 ± 8.6	28.0 ± 9.9	NS
SVRI (d-s/cm^5/m^3)	3,392 ± 1,131	3,122 ± 1,082	NS
PVRI (d-s/cm^5/m^3)	397 ± 278	292 ± 216	0.02
LVSWI (g-m/beat/m^2)	26.0 ± 11.9	30.1 ± 13.8	NS
BP systolic (mm Hg)	134 ± 24	124 ± 22	0.007
BP diastolic (mm Hg)	82 ± 15	78 ± 14	NS
Heart rate (beat/min)	94 ± 14	89 ± 19	NS
Height (m)	1.74 ± 0.11	1.73 ± 0.11	NS
Weight (kg)	129.5 ± 27.1	70.5 ± 13.3	0.00001
BMI (mg/kg^2)	42.4 ± 7.0	23.6 ± 3.4	0.00001

Values are expressed as mean ± SD.
Abbreviations as in Table II.

Characteristics of the obese group: A detailed analysis of obese patients showed that they usually presented with moderately severe heart failure (New York Heart Association functional class II or III) with a mean echocardiographic diastolic dimension of 6.6 ± 0.9 cm, and a mean ejection fraction by catheterization or gated blood pool scan of 25 ± 14%. There was a lifelong history of obesity in 25 (58%) of the patients and 18 (42%) had a history of hypertension. Only 1 patient had a known history of sleep apnea. There were no cases of thyroid disease or pheochromocytoma discovered on evaluation. Three of the 21 patients who underwent coronary angiography had coronary artery disease as defined by the presence of at least 1 stenosis of >50%; 2 patients had 1-vessel and 1 patient had 3-vessel disease. At the time of biopsy, 30 patients (70%) were being treated with cardiac medications. Eighteen patients (42%) were taking digoxin, 27 (63%) a diuretic, 26 (60%) an angiotensin-converting enzyme inhibitor, 6 (14%) nitrates, and 2 (5%) a calcium antagonist.

The most frequent finding on endomyocardial biopsy was myocyte hypertrophy, which was seen in 29 (67%) of the obese patients. Only 1 biopsy showed myocarditis (2%).

Final diagnosis (Table IV): Cardiac evaluation showed that 10 obese patients (23.3%) had a specific etiology for their cardiomyopathy and 33 patients (76.7%) were considered to have "idiopathic" dilated cardiomyopathy. These results are compared to the 409 lean patients in whom a specific etiology was found in 264 patients (64.5%) after a similar evaluation for cardiomyopathy. Only 145 lean patients (35.5%) were considered to have idiopathic dilated cardiomyopathy (p ≤0.0001, chi-square).

The specific diagnoses made in the obese group are listed in Table IV. In the extramyocardial category there were 3 cases of ischemic cardiomyopathy. In the heredofamilial category there were 3 cases of familial cardiomyopathy, including 2 sisters. Only 1 case of alcoholic cardiomyopathy was seen and listed in the toxic reactions category. There was 1 case each of restrictive and nondilated cardiomyopathy.

TABLE IV Final Diagnosis by Weight Category

Diagnosis	Obese n(%)	Lean n(%)
Idiopathic dilated cardiomyopathy	33 (76.7%)	145 (35.5%)
Extramyocardial	3 (7.0%)	55 (13.4%)
Myocarditis	1 (2.3%)	72 (17.6%)
Metabolic	0	18 (4.4%)
Systemic	0	14 (3.4%)
Heredofamilial	3 (7.0%)	8 (2.0%)
Toxic reactions	1 (2.3%)	24 (5.9%)
Peripartum	0	17 (4.2%)
Human immunodeficiency virus	0	14 (3.4%)
Neoplastic	0	4 (0.9%)
Arrhythmia	0	20 (4.9%)
Nondilated cardiomyopathy	1 (2.3%)	12 (2.9%)
Restrictive	1 (2.3%)	6 (1.5%)
Total	42	409

Table IV also lists the specific diagnoses found in the lean group. There were 3 cases of hyperthyroidism, 2 cases of hypothyroidism, 3 cases of cardiac hemochromatosis, and 10 cases of cardiac amyloidosis listed in the Metabolic category. In the Systemic category there were 3 cases of mixed connective tissue disease, 2 cases of progressive systemic sclerosis, 1 case of polyarteritis nodosa, 5 cases of systemic lupus erythematosis, 2 cases of cardiac sarcoidosis and 1 case of rheumatic heart disease. There were 7 cases of familial cardiomyopathy and 1 neuromuscular disorder associated with cardiomyopathy listed in the Heredofamilial category. In the Toxic reactions category there were 6 cases of anthracycline cardiotoxicity, 12 cases of alcoholic cardiomyopathy, 3 cases of cocaine cardiomyopathy, 2 cases of lithium toxicity and 1 case of leukotriene cardiomyopathy. In the Arrhythmia category there were 11 cases of ventricular tachycardia, 5 cases of supraventricular tachycardia and 4 cases of heart block. There were 7 cases of hypertensive cardiomyopathy, 36 cases of ischemic cardiomyopathy, 7 cases of valvular cardiomyopathy, 1 case of cardiomyopathy associated with congenital heart disease, and 4 cases of cardiomyopathy following coronary artery bypass surgery — all listed in the Extramyocardial category.

In the obese group, a specific diagnosis was made by endomyocardial biopsy in only 1 patient (2.3%). In the lean group, a specific diagnosis was made on endomyocardial biopsy in 98 (24%) patients ($p = 0.001$). The specific diagnoses made on endomyocardial biopsy in the lean group were myocarditis, hemochromatosis, amyloidosis, sarcoidosis, rheumatic heart disease, anthracycline cardiotoxicity and cardiac neoplasm.

Complications of endomyocardial biopsy: In the obese group, there were no complications of endomyocardial biopsy that required treatment: 3 episodes of transient supraventricular tachycardia and 1 episode of nonsustained ventricular tachycardia occurred during the procedure and resolved spontaneously. The carotid artery was punctured with the local anesthesia needle in 1 case without causing a hematoma. There was 1 episode of transient atrioventricular block.

DISCUSSION

Endomyocardial biopsy: The endomyocardial biopsy findings in a group of markedly obese patients with established congestive heart failure have not been previously reported. In this study of 43 markedly obese patients, only 1 specific diagnosis was made by endomyocardial biopsy. In this study, endomyocardial biopsy was a safe procedure in the obese patient group. However, it provided fewer histologic diagnoses than in lean patients. Endomyocardial biopsy should therefore be reserved for obese patients in whom there is a high degree of suspicion for the presence of a secondary cardiomyopathy. No etiology was found in 76.7% of the obese patients after a comprehensive evaluation for causes of cardiomyopathy. This is in marked distinction to the lean patients for whom a cause for the cardiac disorder was found in 64.5% of cases. There was a surprisingly low incidence of ischemic cardiomyopathy in the obese group.

Hemodynamics: Obesity is a state of volume overload associated with an elevated cardiac output but a normal cardiac index.[10-14] In this study, cardiac output and right heart filling pressures were significantly correlated with body mass index. We found the cardiac index, which corrects for body surface area, to be similarly decreased in both the obese and the lean groups. Our patients, unlike those in previous studies,[10-14] presented with congestive heart failure and an established dilated cardiomyopathy.

Systemic hypertension is a frequent finding in obesity.[4,11] Our patients were usually normotensive, or treated with afterload reduction therapy. However, 42% did have a history of hypertension, which was not considered to be severe enough to cause the dilated cardiomyopathy. It is impossible, in this study, to determine the relative role hypertension played in the development of cardiomyopathy.

The pulmonary vascular resistance index was significantly higher in the obese subjects. This may reflect intrinsic pulmonary disease, worse left ventricular dysfunction, body habitus, or undiagnosed causes of pulmonary hypertension such as sleep apnea. Only 1 obese patient had a clinically apparent hypoventilation syndrome. Sleep apnea is not known to cause left ventricular dysfunction and cannot account for the cardiomyopathy seen in the obese patients.

Study limitations: We used the Quetelet body mass index as an index of obesity. When compared with hydrostatic determination of percent body fat, the body mass index has yielded correlation coefficients ranging from 0.67 to 0.85.[9] We defined obese as a body mass index ≥ 35 kg/m^2, which correlates to at least 36 kg of excess body fat.[15] We excluded patients with a body mass index ≥ 30 kg/m^2 but <35 kg/m^2 in order to avoid contamination of the obese group with persons displaying moderate obesity. Body mass index does not reflect regional distribution of body fat, which is important in risk stratification, or age-related changes in body composition and is unable to distinguish fat from muscle, bone or edema.[8,9,16] The limitations of endomyocardial biopsy are well known.[17] Finally, this study does not include long-term follow-up or standardized treatment approach.

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Transesophageal Echocardiographic Diagnosis of Right-Sided Cardiac Masses in Patients with Central Lines

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Transesophageal echocardiography provides excellent images of intracardiac masses; however, its use among a series of patients with central venous lines has not been fully described. Nineteen patients (aged 52 ± 16 years; 10 women) had masses detected by transesophageal echocardiography in the presence of a permanent (0.2 to 16 years) pacing wire (n = 8), and a current (n = 9) or recent (n = 2) (1 to 281 days) indwelling catheter. Transthoracic echocardiography suggested the presence of a mass in 5 patients (26%), although in only 2 cases were its findings consistent with transesophageal findings. Transesophageal echocardiography indicated the presence of a mass in or near the superior vena cava in 13 patients, in the right atrium in 6, and adjacent to the tricuspid valve in 3. Discrete masses measured 1.6 ± 2.1 cm^2 in area during transesophageal echocardiography. Eleven patients had positive blood cultures, 7 with staphylococcal species. Mass size was not significantly altered by the type of line or sepsis, but showed a weak correlation with line age ($r = 0.56$). Transesophageal echocardiography altered the management of 9 patients, prompting surgery (n = 3) and line removal (n = 3), and antibiotic (n = 2) or anticoagulation (n = 3) therapy.

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Central venous lines promote the formation of thrombi and vegetations in the right heart by damaging endocardium.[1-4] This may lead to sequelae as pulmonary embolism,[5] persistent sepsis and valve destruction.[6-9] Transthoracic echocardiography is limited in its ability to detect intracardiac masses and may not provide an early antemortem diagnosis. However, the ability of transesophageal echocardiography to image masses, particularly in the posterior heart, has been well documented.[10,11] The purpose of this study was to determine the clinical and transesophageal echocardiographic features of right heart masses attributable to central venous lines.

METHODS

Patients: From the records of 2,466 consecutive transesophageal echocardiograms, 19 patients were identified with central venous lines and masses in the right heart. Charts were reviewed for the patient's diagnosis, overall clinical condition, and type and age of right heart line inserted. Four patients also had surgical or autopsy confirmation of the ultrasound findings.

Technique of transesophageal imaging: The technique of transesophageal echocardiographic examination in awake patients that was used in all patients was previously described.[12-14] A 5 MHz transducer with 64 crystals and 1 of several imaging systems (Hewlett-Packard 77020ac or SONOS 1000, Andover, Massachusetts; Acuson 128, Mountainview, California; or ATL Ultramark 9, Bothell, Washington) were used in 18 patients. Biplane transesophageal echocardiography[15-17] was performed in 1 patient, using two 5 MHz transducers with 48 crystals and an ATL Ultramark 7 machine.

In most cases, transthoracic echocardiography was performed with a Hewlett-Packard imaging system and a 2.5 MHz transducer from standard parasternal, apical, subcostal and suprasternal views. The transthoracic study was performed within a week of the transesophageal examination in 16 patients and within 3 months in 3 patients.

Two observers reviewed the video recordings of the surface and transesophageal studies to determine whether the images strongly suggested that a mass was present. In each study, the largest mass area was measured by planimetry using the measurement package of a Hewlett-Packard SONOS 1000.

Statistical analysis: Values are expressed as mean ± SD. Correlations between maximal mass area and line age were obtained by linear regression analysis. The effect of line type (catheter vs pacing wire) or presence of

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septicemia on the size of the mass was assessed using an unpaired Student's *t* test. Statistical significance was assumed with a p value <0.05.

RESULTS

Clinical data: Nineteen patients (9 men and 10 women, aged 52 ± 16 years, range 26 to 82) had images of right heart masses related to central venous lines. Eight patients had permanent pacing wires (dual-chamber in 4) for 2 months to 16 years. Eleven patients had central venous catheters, with infusion of total parenteral nutrition in 4 patients. These lines were in place for <1 month, except in 2 patients with lines of 8 and 10 months old. In 2 patients, venous catheters were removed immediately before transesophageal echocardiography was performed.

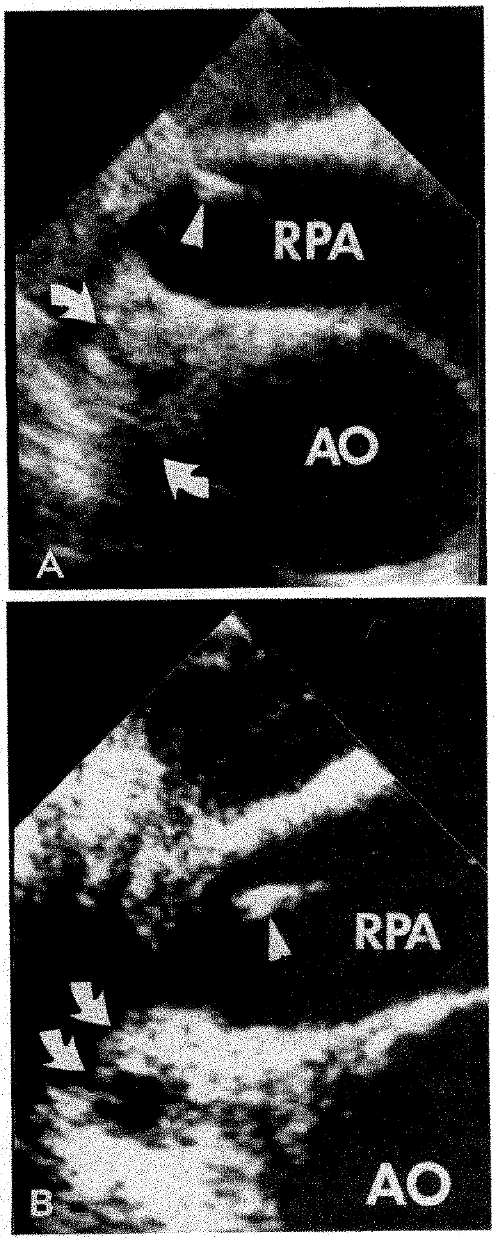

FIGURE 1. ***A,*** **transesophageal short-axis view of thrombus *(between arrows)* in superior vena cava around Swan Ganz catheter. *B,* patient's superior vena cava syndrome subsided with anticoagulation and changing site of line insertion to femoral vein. Superior vena cava appears more patent *(arrows)* in this similar view. Residual thrombus in superior vena cava was present during autopsy. Catheter in right pulmonary artery (RPA) *(arrowheads).* AO = aorta.**

Patients were referred for echocardiographic examination to diagnose endocarditis (n = 12), evaluate left ventricular function (n = 2) and assess prosthetic valve function (n = 2). The remaining studies were performed to detect an atrial septal defect, an intracardiac source of embolism and the cause of atrial fibrillation.

Most patients were seriously ill at the time of transesophageal echocardiography; 17 were inpatients (including 8 in the intensive care unit), and 2 were outpatients. Eleven of 19 patients had proven septicemia. Blood cultures grew staphylococcus aureus or epidermidis in 7 patients. Seven patients had recent surgery (cardiac in 4). Serious bowel pathology was present in 8 patients. Five patients had myocardial infarction (4 recently), 3 with right ventricular involvement.

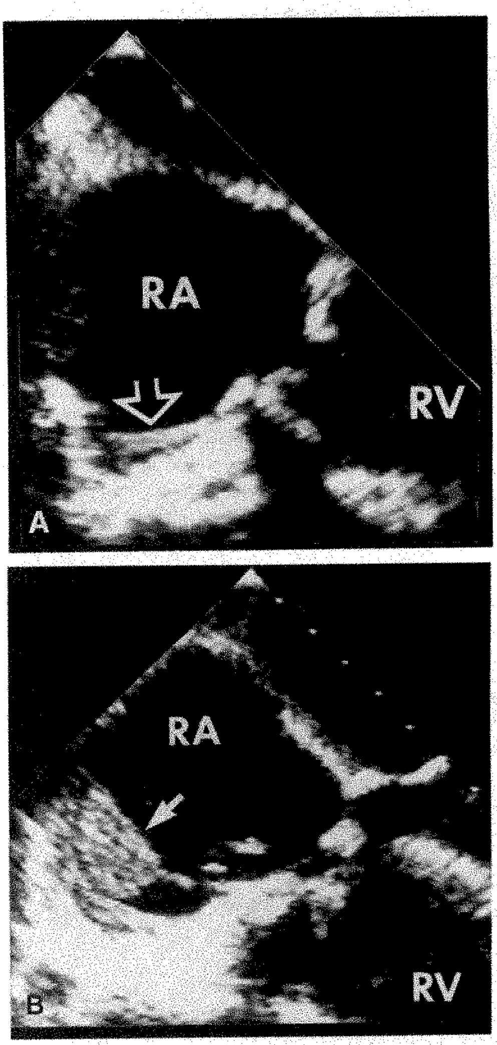

FIGURE 2. Transesophageal echocardiographic demonstration of growth of mural thrombus in patient with right heart failure after right ventricular infarction, tricuspid valve replacement and recurrent supraventricular arrhythmias. *A,* mural right atrial thrombus *(open arrow). B,* 2 years later, second thrombus formed *(arrow),* as confirmed surgically. Pacing wire (not shown) is in another imaging plane. RA = right atrium; RV = right ventricle.

Transthoracic findings: Transthoracic echocardiography suggested the presence of a mass in only 5 patients (26%). However, the transthoracic description of the mass was consistent with transesophageal findings in only 2 patients. These 2 patients had medium to large masses localized in the right atrium near the tricuspid valve. In the other 3 patients, a prominent tricuspid valve annulus and tangential views of pacing wires were misinterpreted as masses during transthoracic imaging. Masses in or near the superior vena cava were not detected until transesophageal echocardiography was performed. Fourteen patients had negative transthoracic studies due to suboptimal images of the right-sided heart (n = 5) or the location of the mass in or near the superior vena cava (n = 13). Five patients had significant tricuspid regurgitation or right heart dilatation.

Transesophageal findings: Transesophageal echocardiography clearly defined right heart masses according to mobility, location and size. Sessile masses were identified in the superior vena cava (n = 4) (Figure 1) and along the right atrial free wall (n = 3) (Figure 2). Pedunculated masses, found in 15 patients, showed mobility independent of the motion of adjacent structures. These masses were located near or in the superior vena cava (n = 9), on the right atrial free wall (n = 3) or near the tricuspid annulus (n = 3). Two patients had >1 mass (Figure 3). Transesophageal echocardiography was able to image very small masses (millimeters in length or width). Masses appeared miniscule (area <0.2 cm^2) in 6 patients, small (0.2 to 0.9 cm^2) in 5, medium sized (1 to 3 cm^2) in 5, and large (>3 cm^2) in 3. Mass size was not significantly affected by the type of central line or presence of sepsis, but had a weak correlation with the line's age ($r = 0.56$). One patient had a mobile strand of 1.3 cm long attached to a Swan Ganz catheter inserted the previous day. Biplane transesophageal imaging in another patient detected a nodular mass at the junction of the superior vena cava and right atrium, which was not distinctly visible with transverse imaging alone (Figure 4).

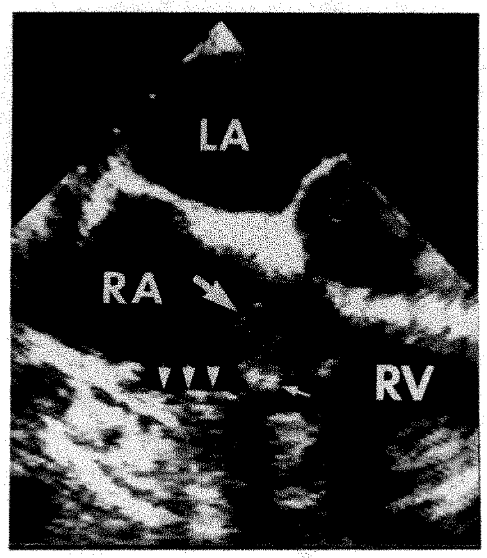

FIGURE 3. Transesophageal echocardiographic 4-chamber view of multilobulated vegetation *(large arrow)* associated with 16-year-old pacing wire *(small arrow)*. Patient had pulmonary embolism, as well as fever of unknown origin and cachexia during 1-year period until this study, and staphylococcus epidermidis septicemia prompted surgery. *Arrowheads* point to mural thrombus in right atrium (RA). LA = left atrium; RV = right ventricle.

Management: On the basis of transesophageal findings, 9 of 19 patients were managed differently. In 3 patients, surgery was prompted and guided by transesophageal echocardiography. These studies were validated by the finding of thrombus during surgery. Transesophageal echocardiography also prompted line removal in 3 patients. In 1 patient, the motion of a mass was monitored while a venous catheter was being removed to detect the possible dislodgement of the mass.

Transesophageal echocardiography also prompted changes in anticoagulation (n = 3) and antibiotic

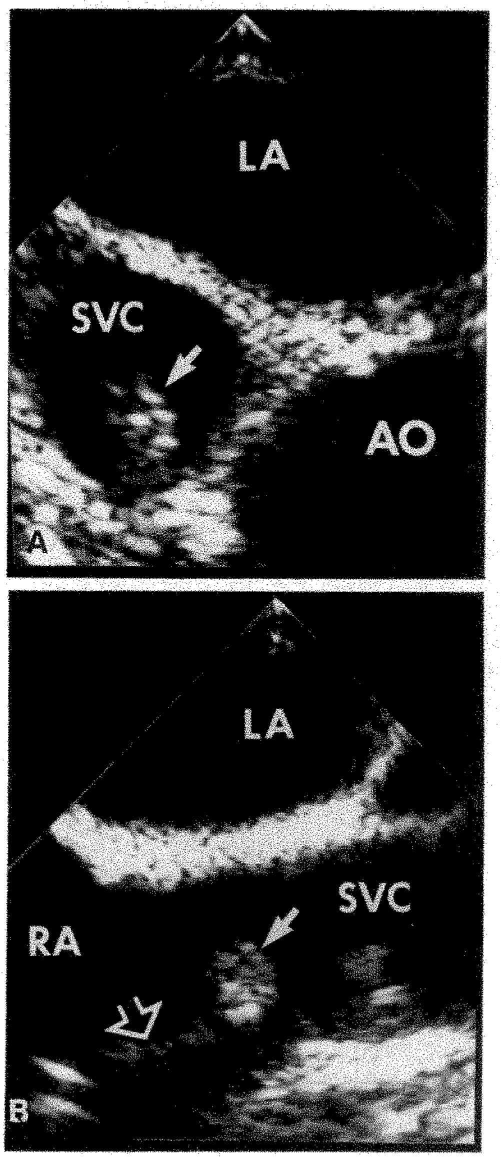

FIGURE 4. Demonstration of use of biplane transesophageal echocardiography for detection of mass in superior vena cava (SVC). *A,* transverse view suggests thickening *(arrow)* of 10-month-old Portacath catheter in 32-year-old woman with intestinal dysmotility, nightsweats and remote staphylococcal epidermidis septicemia. *B,* during longitudinal imaging, small sessile mass *(arrow)* is detected adjacent to line *(open arrow)*. AO = aorta; LA = left atrium; RA = right atrium.

(n = 2) therapy. Most patients with sepsis received antibiotics for ≥3 weeks, with resolution of a mass documented on a second transesophageal study in 1 patient. Vancomycin and gentamicin were the most frequently used antibiotics. Eight patients (42%) died within 2 months of the transesophageal examination.

DISCUSSION

This investigation demonstrates the clinical and echocardiographic features of a series of patients with central venous lines and right heart masses. This complication is not often detected. Our records indicate that ≥8% of our transesophageal studies were performed in patients with central lines; of these, 10% (n = 19) had right-sided masses. Transesophageal images were clearly superior to the transthoracic views, especially for interrogation of the superior vena cava.[10,18] Suboptimal image quality was the most important limitation of transthoracic imaging, which was accurate in only 2 patients. Alternatively, transesophageal echocardiography localized thrombi and vegetations, and characterized them according to size and mobility.[10,11,19]

This study also describes the clinical use of transesophageal imaging in patients with central lines. In addition to right-sided masses, transesophageal echocardiography was useful in diagnosing other sequelae of central lines as tricuspid valve endocarditis[6–9] and stenosis,[20] right atrial mural thrombosis[21,22] and superior vena caval obstruction.[23]

Many cases that constituted the study group had unique features. In 1 patient, a right atrial mural mass grew over a period of years, whereas in another, the mass formed quickly on a central line within a day of its insertion. Masses varied considerably in size, but even very small masses (millimeters long) could be detected by transesophageal imaging.[24] Biplane transesophageal echocardiography improves the examination of the superior vena cava,[16–18] and this was evident in 1 patient where the longitudinal plane was more diagnostic than was transverse imaging alone.

Transesophageal echocardiography was important in guiding the management of patients. Transthoracic imaging alone usually did not exclude the diagnosis of endocarditis or thromboembolism. Whereas the clinical service occasionally depended heavily on transesophageal findings, almost half of the patients died soon after the study. With a few important exceptions, it would be difficult to assume that diagnosis changed outcome for most patients.

Limitations of echocardiography: High gain setting, reverberation and lateral resolution artifact increase the risk of an incorrect diagnosis.[21] Transesophageal echocardiography (even when biplane) is restricted in the number of views it can obtain.[17] Thus, characterizing the attachment of a mass to a central line was occasionally difficult. Right atrial dilatation is another factor that can reduce the quality of transesophageal images by positioning some masses in the far field of the ultrasonic beam.

Echocardiography does not definitively provide a histologic diagnosis, although surgery or autopsy provided validation in 4 patients. In the remaining patients, echocardiographic findings and the clinical course strongly suggested that an intracardiac mass consisted of thrombus or vegetation and not tumor, artifact, or normal anatomical structure. This study presumes that masses formed in situ due to the central line, stasis of blood, a hypercoagulable state and sepsis. Whereas venous embolism to the right heart may have occurred, no mass had the typical serpiginous appearance of a thromboembolus and only 2 patients had history of phlebitis.[5,21,22]

Although several risk factors were usually present for the formation of right heart masses in patients with central lines, serious illness may not be prerequisite. One patient was very active and only mildly symptomatic from an atrial septal defect. In a healthy subject, fibrin strands on a pacing wire may not cause much clinical concern. The danger of a right-sided cardiac mass relates to its size and mobility, and whether it is infected.[19] An infected mass can cause valve destruction, whereas a mobile mass may embolize to the lungs, or through a patent foramen ovale to the systemic circulation.[5–9,25] These considerations may influence patient management decisions.

Transesophageal echocardiography should be considered in patients with central lines and sepsis or thromboembolism of unclear etiology, even if there are no other risk factors for a right-sided cardiac mass. When transthoracic echocardiography demonstrates a mass in the right heart, transesophageal echocardiography may be useful for verification, clearer characterization of the mass, and visualization of the superior vena cava.

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Left Ventricular Response to Submaximal Exercise in Endurance-Trained Athletes and Sedentary Adults

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This investigation examines the hypothesis that athletes increase stroke volume with submaximal exercise through an augmentation of left ventricular (LV) end-diastolic volume and a reduction of LV end-systolic volume, whereas sedentary adults only increase stroke volume modestly, because LV end-diastolic volume does not increase. Upright bicycle exercise was performed by 17 endurance-trained male athletes and 15 sedentary men. M-mode echocardiograms were obtained during submaximal exercise at predetermined heart rates. Athletes, at a heart rate of 130 beats/min, increased their stroke volume 67% from 72 ± 18 ml to 120 ± 26 ml ($p < 0.001$). This resulted from an increase of LV end-diastolic volume from 119 ± 23 to 152 ± 28 ml ($p < 0.001$) and a reduction in LV end-systolic volume from 46 ± 14 to 31 ± 9 ml ($p < 0.001$). Sedentary men at the same heart rate increased stroke volume 22% from 63 ± 15 to 77 ± 21 ml ($p < 0.05$). LV end-diastolic volume did not change (96 ± 20 vs 97 ± 28 ml) (p = not significant), but LV end-systolic volume decreased (33 ± 11 vs 20 ± 9 ml) ($p < 0.001$). In conclusion, athletes increased cardiac output through a more prominent augmentation of stroke volume than sedentary subjects at submaximal exercise. This was accomplished through an augmentation of LV end-diastolic volume. This may have a conserving effect on myocardial oxygen consumption at these levels of exercise.

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The mechanism of the greater response of stroke volume in exercise among athletes than in untrained healthy adults is undetermined. Our previous work, and the investigations of some others, suggests that there may be a difference in the response of left ventricular (LV) end-diastolic volume,[1,2] but there is no uniform agreement on this.[3] In the present investigation we tested the hypothesis that stroke volume increases more prominently with upright exercise in athletes than in untrained adults because of differences in the response of LV end-diastolic volume.

METHODS

Study group: Seventeen male athletes underwent cardiovascular evaluations. Eight of the athletes were members of a university swim team and 9 were competitive cyclists at state or national levels. Measurements were compared with 15 sedentary men. Fourteen of 15 sedentary subjects exercised <1 hour/week. The remaining subject played noncompetitive singles tennis 3 times weekly. All athletes and sedentary subjects were free of known cardiac disease and took no cardiac medications.

Exercise protocol: All the athletes and sedentary subjects exercised submaximally on a stationary bicycle in the semierect position. Each participant exercised in 3-minute stages at heart rates of 110, 130 and 150 beats/min. At rest, sitting on the bicycle, and at each specified heart rate (110, 130 and 150 beats/min), measurements were obtained of blood pressure, cardiac dimensions by M-mode echocardiography, and external work performed.

Measurements: Echocardiographs (Hewlett Packard 500 system) were obtained in athletes and sedentary subjects while on a bicycle in the semierect position during held expiration at rest and during each preestablished stage of exercise. Measurements were obtained from the M-mode echocardiograms as described previously.[2]

Blood pressure in the arm was measured by the Karotkoff method at rest and during each stage of exercise. External work per minute (W) was measured on a stationary bicycle by calculating the work required to rotate a flywheel at various measured rates, averaged over 1 minute, and taking into account gear ratios.

Statistical analysis: Temporal changes of echocardiographic measurements, blood pressure and power output were compared with resting values using Student's paired t test. For these tests, a probability <0.05 was considered significant. Comparisons were obtained at predetermined heart rates of 110, 130 and 150 beats/

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TABLE I Height, Weight, Age and Resting (supine) Blood Pressure and Heart Rate

	Athletes (n = 17)	Sedentary Subjects (n = 15)	p Value
Height (cm)	179 ± 9	178 ± 6	NS
Weight (kg)	75 ± 6	75 ± 11	NS
Age (year)	24 ± 4	28 ± 3	<0.001
BP (mm Hg)	132/74 ± 11/8	123/70 ± 6/8	<0.02/NS
Heart rate (min^{-1})	62 ± 9	77 ± 14	<0.01

BP = blood pressure; NS = not significant.

min. All data are reported as mean ± standard deviation. Comparisons of athletes with sedentary subjects at each predetermined heart rate were obtained with Student's unpaired *t* test.

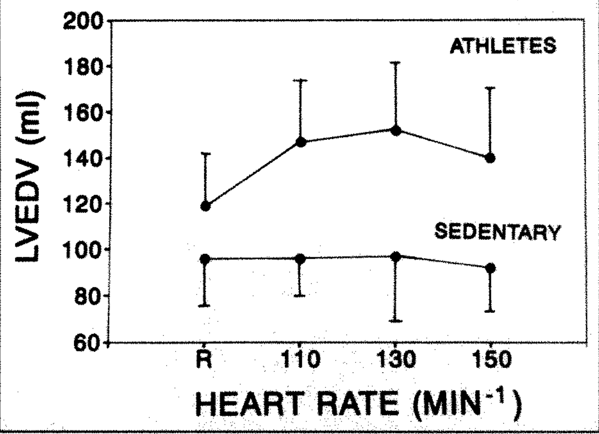

FIGURE 1. Left ventricular end-diastolic volume (LVEDV) at rest (R) and at various heart rates during exercise in athletes and sedentary subjects. Statistics are described in the text and in Table II. Graph shows mean + standard deviation.

RESULTS

The athletes and sedentary subjects were similar in height and weight (Table I). Athletes were somewhat younger, had a lower resting heart rate and higher systolic blood pressure.

At each heart rate, athletes performed approximately twice the work per minute in comparison to sedentary subjects (all differences p <0.001 [Table II]). Systolic blood pressure at each heart rate during exercise was higher among athletes (p <0.001) (Table II). Diastolic pressure was similar in athletes and sedentary subjects and did not change significantly with exercise.

LV end-diastolic volume was higher among athletes than sedentary subjects at rest while sitting on the bicycle (119 ± 23 vs 96 ± 20 ml) (p <0.01) (Table II) (Figure 1). With exercise, as the heart rate increased from resting rates to 110 beats/min, athletes increased their LV end-diastolic volume from 119 ± 23 to 147 ± 27 ml (p <0.001). With further exercise to a heart rate of 130 beats/min there was no significant change. At higher levels of exercise, after heart rate increased from 130 to 150 beats/min, LV end-diastolic volume diminished from 152 ± 28 to 140 ± 31 ml. At all heart rates during submaximal exercise, LV end-diastolic volume was higher in athletes than in sedentary subjects (p <0.001). Among sedentary subjects LV end-diastolic volume did not change with exercise.

LV end-systolic volume was larger in athletes than in sedentary subjects at rest (46 ± 14 vs 33 ± 11 ml) (p <0.01) (Table II) (Figure 2). At heart rates of 110 and 130 beats/min, the significance of the difference of LV end-systolic volume between athletes and sedentary subjects was p <0.01, and at 150 beats/min it was p <0.02. Both athletes and sedentary subjects decreased their LV end-systolic volume with exercise (Table II) (Figure 2).

Athletes had similar stroke volumes as sedentary subjects at rest (72 ± 18 vs 63 ± 15 ml) (p = not significant) (Table II) (Figure 3). At similar heart rates during submaximal exercise, athletes had a larger stroke volume than untrained subjects (p <0.001). Stroke volume among athletes increased prominently from rest to exercise at a heart rate of 110 beats/min (72 ± 18 vs 111 ± 25 ml) (p <0.001). In the athletes, as exercise increased, the stroke volume continued to increase until a heart rate of 130 beats/min was reached. At higher levels of exercise and heart rate, there was no further increase in stroke volume. Sedentary subjects had no significant increase in stroke volume at a heart rate of 110 beats/min, but with exercise sufficient to produce a

TABLE II Left Ventricular Dimensions, Function, Oxygen Consumption, Blood Pressure and Power

	Rest Sitting		Heart Rate					
			110 Beats/Min		130 Beats/Min		150 Beats/Min	
	Athletes (n = 17)	Sedentary (n = 15)	Athletes (n = 17)	Sedentary (n = 15)	Athletes (n = 17)	Sedentary (n = 15)	Athletes (n = 17)	Sedentary (n = 15)
LV end-diastolic volume (ml)	119 ± 23†	96 ± 20	147 ± 27*§	96 ± 16	152 ± 28*§	97 ± 28	140 ± 31*‖	92 ± 18
LV end-systolic volume (ml)	46 ± 14†	33 ± 11	36 ± 11†‖	25 ± 7‖	31 ± 9†§	20 ± 9§	23 ± 9‡§	16 ± 4§
Stroke volume (ml)	72 ± 18	63 ± 15	111 ± 25*§	71 ± 17	120 ± 26*§	77 ± 21¶	117 ± 27*§	76 ± 16¶
Cardiac output (liters/min)	5.2 ± 1.2	5.6 ± 1.5	12.2 ± 2.7*§	7.8 ± 1.9‖	15.7 ± 3.3*§	10.0 ± 2.8§	17.5 ± 4.1*§	11.4 ± 2.4§
Ejection fraction (%)	61 ± 9	66 ± 8	75 ± 6§	72 ± 10¶	79 ± 5§	80 ± 5§	84 ± 6§	82 ± 3§
Blood pressure systole (mm Hg)	134 ± 12†	121 ± 7	178 ± 14*§	147 ± 13§	196 ± 15*§	169 ± 17§	208 ± 18*§	177 ± 18§
Blood pressure diastole (mm Hg)	85 ± 10	79 ± 8	84 ± 12	85 ± 10	82 ± 10	83 ± 7	79 ± 11¶	82 ± 11
Mechanical power output (W)	—	—	99 ± 33*	47 ± 25	149 ± 42*	70 ± 30	193 ± 47*	94 ± 36

Athletes versus sedentary subjects: *p <0.001; †p <0.01; ‡p <0.02.
Exercise versus rest: §p <0.001; ‖p <0.01; ¶p <0.05.

heart rate of 130 beats/min, stroke volume increased from a resting rate of 63 ± 15 to 77 ± 21 ml ($p < 0.05$). With further exercise, stroke volume had no further change.

Cardiac output at rest was similar in athletes and sedentary adults (Table II). At all levels of exercise, athletes had a higher cardiac output than sedentary subjects (all $p < 0.001$). Both athletes and sedentary subjects increased their cardiac output at a heart rate of 110 beats/min (athletes $p < 0.001$, sedentary $p < 0.01$), and differences were maintained, compared with rest, at higher levels.

The ejection fraction at rest and during all levels of exercise at the respective heart rates did not differ significantly among athletes and sedentary subjects (Table II) (Figure 4). With exercise, both athletes and sedentary subjects had an increased ejection fraction.

DISCUSSION

Athletes increased cardiac output through a prominent increase in stroke volume as well as in heart rate. Sedentary subjects had a less prominent increase in stroke volume. It is generally recognized that training results in a higher stroke volume with exercise than occurs in untrained healthy adults.[1,2,4-6] Various temporal changes in stroke volume during exercise have been described.[7] Stroke volume may increase continuously throughout exercise, level off or decrease with increasing exercise.[7]

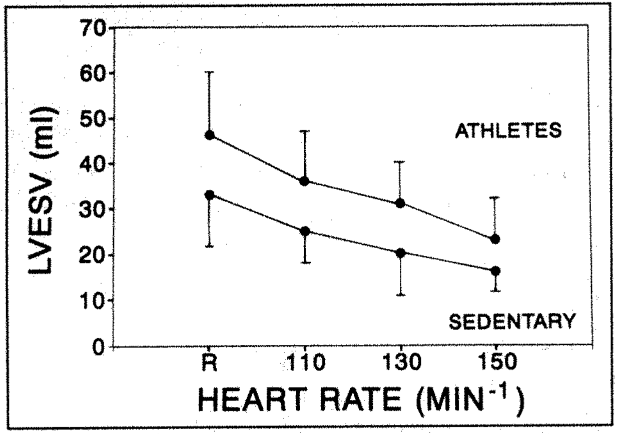

FIGURE 2. Left ventricular end-systolic volume (LVESV) at rest (R) and various heart rates during exercise. Statistics are described in the text and in Table II. Graph shows mean + standard deviation.

The increased stroke volume in athletes resulted from an augmentation LV end-diastolic volume and a reduction of LV end-systolic volume. Sedentary subjects had only a reduction of LV end-systolic volume, with no augmentation of end-diastolic volume. Our previous study showed a trend toward an increased LV end-diastolic volume with exercise in athletes.[2] Measurements, however, were obtained just after exercise, and in a supine position, which may attenuate the response of stroke volume to exercise.

LV end-diastolic volume during upright exercise in untrained subjects has been reported to increase,[8-10] show no change,[1,11] or show no change except a decline at maximal exercise.[3] LV end-diastolic volume in untrained subjects during supine exercise or while supine immediately after exercise has been reported to increase,[10,12] show no change[6,13-16] or decrease.[2,17,18]

LV end-systolic volume in untrained subjects during upright exercise has been reported to decrease,[1,3,8,11] except in the elderly.[9] LV end-systolic volume in untrained subjects during supine exercise or while supine immediately after exercise has been shown to decrease[2,6,10,13,15,17,19] or show no change.[12,14]

Regarding athletes, LV end-diastolic volume during upright exercise increased with submaximal exercise.[1,3] At peak exercise, however, Ginzton et al[3] observed a decrease in LV end-diastolic volume below resting values in athletes and sedentary subjects, whereas Rubal et al[3] observed only a slight decline. In athletes, we observed a reduction in LV end-diastolic volume at a heart rate of 150 beats/min, compared with a heart rate of 130 beats/min. Such a reduction in LV end-diastolic volume may have resulted from limited diastolic filling due to a shortened diastolic filling time. Supine exercise or measurements in a supine position immediately after exercise in endurance trained athletes usually showed no change in LV end-diastolic volume.[2,10,16] However, an increased[6] or a trend toward an increasing[2] LV end-diastolic volume as well as a decreased LV end-diastolic volume[17] have been reported.

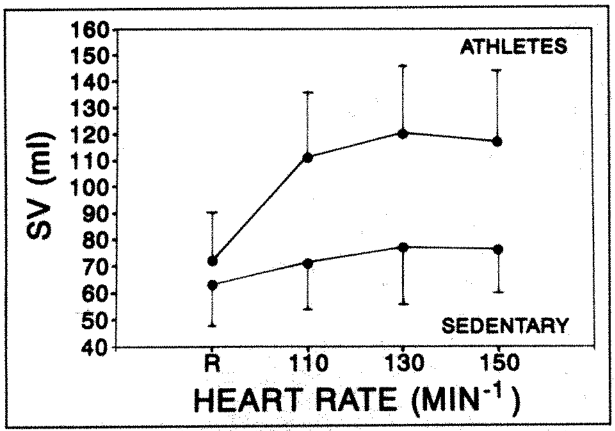

FIGURE 3. Stroke volume (SV) at various heart rates during exercise. Statistics are described in the text and in Table II. Graph shows mean + standard deviation. R = rest.

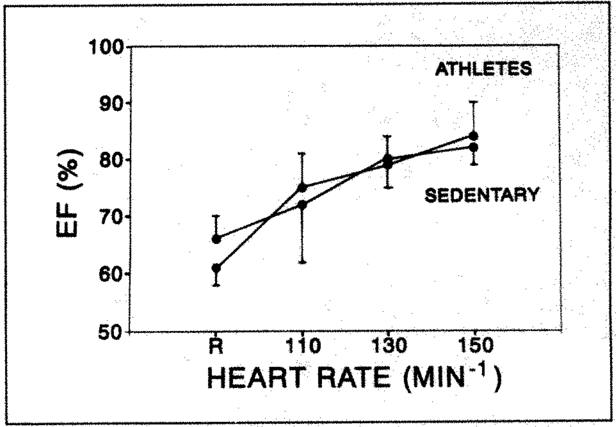

FIGURE 4. Ejection fraction (EF) at various heart rates during exercise. Statistics are described in the text and in Table II. Graph shows mean + standard deviation. R = rest.

Among athletes during upright exercise, LV end-systolic volume decreased,[3] or showed a trend toward decreasing.[1] During supine exercise or while supine immediately after exercise, LV end-systolic volume in athletes decreased[2,10] or showed a trend toward decreasing.[1]

Myocardial oxygen consumption is less dependent on stroke volume than on heart rate.[20] Athletes, therefore, by increasing cardiac output with submaximal exercise through a prominent increase in stroke volume as well as heart rate, may require less myocardial oxygen than if cardiac output were increased by heart rate alone. At maximal exercise, when LV filling time is greatly shortened, this effect may not be present.

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Prognostic Value of Echocardiography in Hospitalized Patients with Pericardial Effusion

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Mohammad Ali Saniei, MD, and Nelson B. Schiller, MD

It is often difficult to predict outcome in hospitalized patients with pericardial effusion. To address this issue, the prognostic value of echocardiography was studied in 187 hospitalized patients diagnosed with pericardial effusions over a 1-year period. The index echocardiogram showed that 11 effusions were large (6%), 39 were moderate (21%), and 137 were small (73%). Right ventricular collapse was present in 7% of cases (13 of 178), right atrial collapse in 12% (21 of 168), and inferior vena cava (IVC) plethora with blunted response to respiration in 35% (46 of 132). During the course of hospitalization, 9 patients (5%) had cardiac tamponade and 16 (9%) had cardiac tamponade, pericardiocentesis and/or surgical drainage (combined end point). By univariate analysis, each echocardiographic sign was associated with both cardiac tamponade and the combined end point ($p \leq 0.01$ for comparisons with size and right-sided chamber collapse; $p \leq 0.07$ for comparisons with IVC plethora). When the data were analyzed with logistic regression modeling, effusion size was the most powerful predictor of outcome (cardiac tamponade: odds ratio 51, 95% confidence interval 3.5–729, $p = 0.004$; combined end point: odds ratio 78, 95% confidence interval 14–421, $p = 0.0001$), and neither right-sided chamber collapse nor IVC plethora with blunted response to respiration retained significant associations. It is concluded that echocardiographically determined effusion size is a powerful predictor of outcome in hospitalized patients with pericardial effusion, and that right-sided chamber collapse and IVC plethora with blunted response to respiration add little if any additional prognostic information.

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Most pericardial effusions observed in hospitalized patients resolve spontaneously and cause little if any clinical dilemma. Others, however, may lead to hemodynamic impairment and eventually require pericardiocentesis or surgical drainage. It is often difficult to predict which effusions will progress and which will resolve spontaneously. If clinical outcome could be predicted from information available at the time of diagnosis, patients at high risk for progression could be identified and treated aggressively. At the same time, patients at low risk for progression could also be identified, and conservative management could be used with greater assurance. Previous studies identified effusion etiology, rate of fluid accumulation and hemodynamic status as clinical factors that may be helpful in assessing prognosis.[1-5] Echocardiographic signs seen at the time of diagnosis may also provide prognostic information.[6] Right ventricular collapse, right atrial collapse, and inferior vena cava (IVC) plethora with blunted response to respiration are sensitive and specific signs for the diagnosis of cardiac tamponade.[7-16] Because these signs are reflective of hemodynamic impairment, their presence in patients who are not in overt tamponade may help identify those at high risk for progression. To address this issue, we examined the echocardiograms and clinical courses of 187 hospitalized patients with pericardial effusion. Our purpose was to determine the prognostic value of echocardiography in hospitalized patients with pericardial effusion.

METHODS

Patient population: The Moffitt-Long Hospital is a tertiary care medical center that serves as the main teaching hospital for the University of California at San Francisco (UCSF). We assembled a retrospective cohort of 187 consecutive patients from the UCSF Echocardiography Data Base. This cohort comprised all patients who were diagnosed with pericardial effusion by 2-dimensional echocardiography over a 1-year period. Patients came from all medical and surgical services, including the Emergency Department. To be included, patients had to be either hospitalized at the time of the index echocardiogram or admitted to the hospital immediately after the study. If multiple echocardiograms were obtained during an admission, the first to document an effusion was used as the index study.

Two hundred forty-two patients were initially identified as having pericardial effusions. Fifty-five patients were subsequently excluded from the analysis (39 because they were outpatients, 13 because their echocardiograms were technically inadequate or showed questionable evidence of effusion, 2 because their echocar-

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TABLE I Admission Diagnoses of 187 Hospitalized Patients with Pericardial Effusion

	No. (%)
Chest pain/unstable angina/possible myocardial infarction	30 (16)
Cancer complication	26 (14)
Congestive heart failure	16 (9)
End-stage liver disease	14 (7)
Valvular heart disease	11 (6)
End-stage renal failure	11 (6)
Organ transplant complication	10 (5)
Arrhythmia	8 (4)
Complication of acquired immunodeficiency syndrome	7 (4)
Elective bypass surgery	6 (3)
Accessory pathway ablation procedure	5 (3)
Possible sepsis	5 (3)
Heart transplant	4 (2)
Endocarditis	3 (2)
Pericarditis/pericardial effusion/cardiac tamponade	3 (2)
Abdominal pain	2 (1)
Peripheral edema	2 (1)
Gastrointestinal bleeding	2 (1)
Amyloidosis	1 (0.5)
Skin infection	1 (0.5)
Pelvic pain	1 (0.5)
Elective repair of congenital heart condition	1 (0.5)
Nausea/vomiting	1 (0.5)
Stroke	1 (0.5)
Pneumonia	1 (0.5)
Prosthetic valve dehiscence	1 (0.5)
Secondary hyperparathyroidism	1 (0.5)
Exacerbation of chronic obstructive pulmonary disease	1 (0.5)
Aortic dissection	1 (0.5)
Pulmonary atresia	1 (0.5)
Abdominal aortic aneurysm	1 (0.5)
Premature rupture of membranes	1 (0.5)
Jaundice	1 (0.5)
Syncope	1 (0.5)
Hypertension	1 (0.5)
Sudden death	1 (0.5)
Pleural effusion	1 (0.5)
Dysphagia	1 (0.5)
Pathologic fracture	1 (0.5)
Fever of unknown origin	1 (0.5)
Total	187 (100)

TABLE II Etiology of Pericardial Effusion in 187 Hospitalized Patients

Etiology	No. (%)
Idiopathic	83 (45)
Cardiothoracic surgery	21 (11)
Neoplasm	21 (11)
End-stage renal disease	20 (11)
Congestive heart failure	18 (10)
Myocardial infarction	10 (5)
Infection	8 (4)
Accessory pathway ablation procedure	6 (3)
Total	187 (100)

Effusion etiologies were based on clinical and historical data. Very few pericardial effusions were definitively diagnosed by pericardiocentesis or examination of pericardial tissue.

diograms were not available for review, and 1 because echocardiography and a pericardiocentesis had been performed before the patient was transferred from another institution). Thus, data from 187 patients were available for analysis.

Echocardiograms: All patients had 2-dimensional echocardiography. Most patients had transthoracic echocardiographic studies performed in our laboratory, but those with effusions documented during portable or transesophageal echocardiographic studies were also included. Echocardiograms were recorded on half-inch VHS videotape and were subsequently evaluated for the following characteristics: effusion size, right ventricular collapse, right atrial collapse, and IVC plethora with blunted response to respiration.

Effusion size was defined as follows: small, an echo-free space only seen posteriorly; moderate, a circumferential echo-free space ≤1 cm in width at its widest point; and large, a circumferential echo-free space >1 cm in width at any point. (Small effusions were estimated to be <100 ml in volume, moderate 100 to 500 and large >500.) Right ventricular and right atrial collapse were defined as a collapse of $>\frac{1}{3}$ of chamber area in any view. IVC plethora with blunted response to respiration was defined as a decrease of <50% in diameter of the proximal vena cava after a deep inspiration or a "sniff."[9]

Chart review: Charts were reviewed for age, sex, admission diagnosis, presumed etiology of effusion at the time of the index echocardiogram, and the following in-hospital outcomes: cardiac tamponade, pericardiocentesis and surgical drainage. Cardiac tamponade was defined by either: (1) equalization of diastolic pressures documented during cardiac catheterization, (2) increase of systolic blood pressure ≥20 mm Hg after pericardiocentesis, or (3) hemodynamic impairment (heart rate >100 beats/min and systolic blood pressure <100 mm Hg) and clinical diagnosis by an attending physician (n = 4). Because drainage of a small quantity of pericardial fluid may be lifesaving, "diagnostic" and "therapeutic" pericardiocenteses were combined. For the same reason, the few patients who had incidental drainage of their effusions during cardiac surgery were considered as having surgical drainage procedures.

Statistical analysis: Potential echocardiographic predictors of outcome were examined by univariate analysis with chi-square or Fisher's exact test. Predictors attaining a p value ≤0.10 were examined by multivariate logistic regression analysis to see which factors (if any) were associated with in-hospital outcome. The following 2 prospectively determined outcomes were used as dependent variables: (1) cardiac tamponade, and (2) a combined end point that included cardiac tamponade, pericardiocentesis and/or surgical drainage. All analyses were 2-sided, and a p value ≤0.05 was considered significant. Odds ratios are reported with 95% confidence intervals (CI).

RESULTS

Natural history: The patient population comprised 101 men (54%) and 86 women (46%), with an average age of 54 ± 19 years. Patients reflected a broad clinical spectrum, as demonstrated by the distribution of admission diagnoses (Table I) and the presumed etiologies of the effusions at the time of diagnosis (Table II). Index echocardiograms showed that 11 effusions were large (6%), 39 were moderate (21%), and 137 were small (73%). Right ventricular collapse was present in 7% of

TABLE III Clinical and Echocardiographic Characteristics of the 16 Patients with Effusion-Related Outcomes

		Index Echocardiogram			Outcomes*		
No.	Effusion Etiology	RV Collapse	RA Collapse	IVC Plethora	Pericardiocentesis	Surgical Drainage	Cardiac Tamponade
	Large (n = 11)						
1	Neoplasm	–	+	–	1	–	–
2	End-stage renal disease	+	†	†	0	–	0
3	Idiopathic	+	+	†	0	0	0
4	Neoplasm	+	†	+	0	–	0
5	Neoplasm	+	+	+	1	–	1
6	Cardiothoracic surgery	–	+	+	–	7	–
7	Idiopathic	+	+	+	0	0	0
8	Idiopathic	+	†	+	0	12	0
	Moderate (n = 39)						
1	Ablation procedure	–	–	†	0	–	0
2	Ablation procedure	–	†	–	0	–	0
3	Infection	–	–	†	–	3	–
4	Infection	+	+	+	0	–	–
	Small (n = 137)						
1	Infection	–	–	–	–	21	–
2	Myocardial infarction	†	†	†	2	–	–
3	Congestive heart failure	–	–	+	–	7	–
4	Congestive heart failure	–	–	†	–	9	9

*Numbers refer to the number of days between the index echocardiogram and the effusion-related outcome. Outcome on day 0 occurred on same day as index echocardiogram.

†Image not adequate for assessment.

IVC = inferior vena cava; RA = right atrial; RV = right ventricular; + = present; – = absent.

cases when the right ventricle was adequately visualized (13 of 178), right atrial collapse in 12% (21 of 168), and IVC plethora with blunted response to respiration in 35% (46 of 132).

During the course of hospitalization, 9 patients (5%) had cardiac tamponade, 11 (6%) had pericardiocentesis, 8 (4%) had surgical drainage, and 16 (9%) had ≥1 of these outcomes (Table III). Overall mortality was 11% (20 of 187). Almost all outcomes occurred within the first few days after the index echocardiogram (Figure 1). Of 9 patients who had tamponade, 7 were diagnosed on the same day as the index echocardiogram, 1 was diagnosed a day later, and 1 was diagnosed 9 days later. This last patient had a small effusion on the index echocardiogram; the patient subsequently had coronary artery bypass surgery, after which a retrocardiac hematoma (adjacent to the right atrium) developed that was responsible for cardiac tamponade. Of 7 patients who had drainage procedures but never developed cardiac tamponade, most had incidental drainage of their effusions during cardiac surgery that was performed for other reasons.

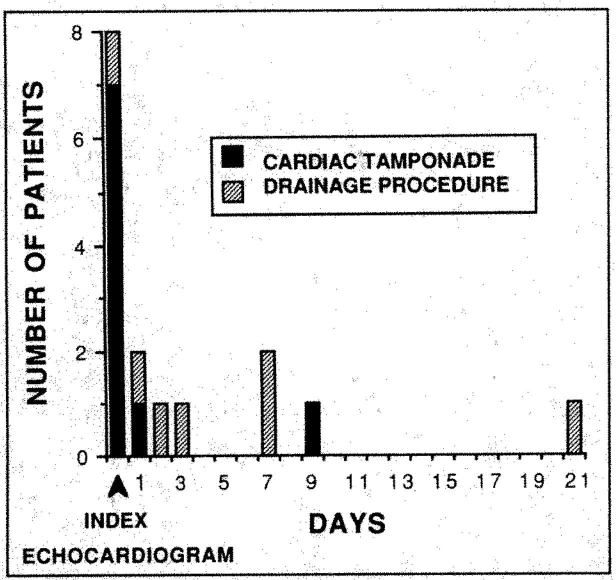

FIGURE 1. Occurrence of cardiac tamponade and pericardial drainage procedures in 187 hospitalized patients with pericardial effusion. Day 0 was the day on which the pericardial effusion was first diagnosed by echocardiography (index echocardiogram). *Solid bars* refer to 9 patients who had cardiac tamponade while in the hospital. *Hatched bars* refer to 7 patients who had drainage procedures, but never developed cardiac tamponade.

Prognostic value of echocardiography: Among patients with large effusions, 73% (8 of 11) had tamponade and/or drainage procedures while in the hospital (Table III) compared with 44% (4 of 39) among those with moderate effusions and 3% (4 of 137) among those with small effusions. Among patients with right ventricular collapse, 54% (7 of 13) had tamponade and/or drainage procedures compared with 29% (6 of 21) among those with right atrial collapse and 15% (7 of 46) among those with IVC plethora with blunted response to respiration.

By univariate analysis, each echocardiographic sign was associated with both cardiac tamponade and the combined end point (Table IV). These associations were present when all 187 patients were examined and when only the 50 with large and moderate effusions were examined. When the echocardiographic signs were examined in a multivariate logistic regression analysis after effusion size was entered, neither right-sided chamber

TABLE IV Univariate and Multivariate Analyses of Echocardiographic Signs and In-Hospital Outcome

	Cardiac Tamponade		Cardiac Tamponade, Pericardiocentesis and/or Surgical Drainage	
	Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
All effusions (n = 187)				
Univariate models				
Size*	215 (20–2,343)	0.0001	78 (14–421)	0.0001
Right ventricular collapse	46 (10–224)	0.0001	23 (6–84)	0.0001
Right atrial collapse	12 (2–77)	0.009	11 (3–42)	0.0003
IVC plethora	8 (1–75)	0.07	5 (1–20)	0.03
Multivariate models				
Size*	51 (4–729)	0.004	78 (14–421)	0.0001
Right ventricular collapse	8 (2–55)	0.04	—	—
Right atrial collapse	—	—	—	—
IVC plethora	—	—	—	—
Large & moderate effusions (n = 50)				
Univariate models				
Size	22 (4–142)	0.001	23 (4–126)	0.0002
Right ventricular collapse	22 (3–138)	0.0012	12 (3–54)	0.002
Right atrial collapse	8 (1–82)	0.09	10 (2–60)	0.01
IVC plethora	10 (1–100)	0.05	9 (2–55)	0.02
Multivariate models				
Size	9 (1–72)	0.04†	23 (4–126)	0.0002
Right ventricular collapse	9 (1–72)	0.04†	—	—
Right atrial collapse	—	—	—	—
IVC plethora	—	—	—	—

*Odds ratios refer to comparisons between patients with large effusions and those with small + moderate effusions.
†There was no significant difference between the multivariate model that included size alone and the model that included both size and right ventricular collapse.
CI = confidence interval; IVC = inferior vena cava.

collapse nor IVC plethora with blunted response to respiration retained significant associations. (In the multivariate model that examined all 187 patients and used cardiac tamponade alone as the end point, right ventricular collapse provided some marginal incremental prognostic information, but this association was not present in the other models.)

Diagnostic value of echocardiography: Although we were principally interested in the prognostic value of echocardiography, we also examined its diagnostic value for cardiac tamponade. We first determined the frequency of right-sided chamber collapse and IVC plethora with blunted response to respiration in patients with different effusion sizes (Table V). Right ventricular collapse, right atrial collapse, and IVC plethora with blunted response to respiration were each seen most frequently in patients with large effusions. Although the frequency of these signs was greatest in patients with large effusions, most effusions seen over the course of the year were small (137 of 187) or moderate (39 of 187). Thus, numerically, many instances of right-sided chamber collapse and IVC plethora with blunted response to respiration occurred in patients with small or moderate effusions. Because very few cases of cardiac tamponade occurred in these patients, the use of these signs to diagnose cardiac tamponade would have resulted in many false positive diagnoses. To evaluate this possibility, we examined the clinical status of patients on the same day as their index echocardiograms (Table VI). Since only 7 patients had cardiac tamponade on the same day as their index echocardiogram, sensitivities could not be adequately determined. However, specificities and predictive values could be assessed, and their values were similar whether all 187 patients were analyzed or whether the analysis was limited to the 50 patients with large and moderate effusions. Specificities for each of the signs were >65%, and negative predictive values were ≥95%, but positive predictive values were <50%.

TABLE V Frequency of Echocardiographic Signs Among Patients with Different Effusion Sizes (%)*

	Effusion Size			
	Large	Moderate	Small	Total
Right ventricular collapse				
Present	7 (64)	4 (11)	2 (2)	13 (7)
Absent	4 (36)	34 (89)	127 (98)	165 (93)
Right atrial collapse				
Present	6 (86)	8 (22)	7 (6)	21 (12)
Absent	1 (14)	28 (78)	118 (94)	147 (88)
IVC plethora with blunted response to respiration				
Present	6 (75)	7 (25)	33 (34)	46 (35)
Absent	2 (25)	21 (75)	63 (66)	86 (65)

*Includes only patients with adequate echocardiographic images for assessment.
IVC = inferior vena cava.

DISCUSSION

This study investigated the prognostic value of echocardiography in a group of hospitalized patients with pericardial effusion. We found that clinically significant

TABLE VI Diagnostic Value of Echocardiography for Cardiac Tamponade (%)*

	Specificity	Positive Predictive Value	Negative Predictive Value
All patients (n = 187)			
Large pericardial effusion	174/180 (97)	5/11 (45)	174/176 (99)
Right ventricular collapse	163/171 (95)	5/13 (38)	163/165 (99)
Right atrial collapse	146/165 (88)	2/21 (10)	146/147 (99)
IVC plethora with blunted response to respiration	85/128 (66)	3/46 (7)	85/86 (99)
Patients with moderate & large effusions (n = 50)			
Large pericardial effusion	37/43 (86)	5/11 (45)	37/39 (95)
Right ventricular collapse	36/42 (86)	5/11 (45)	36/38 (95)
Right atrial collapse	28/40 (70)	2/14 (14)	28/29 (97)
IVC plethora with blunted response to respiration	22/32 (69)	3/13 (23)	22/23 (96)

*Data were derived from the clinical status of patients on same day as their index echocardiograms. Sensitivity could not be adequately assessed, because only 7 patients were diagnosed with cardiac tamponade on same day as their index echocardiogram.
IVC = inferior vena cava.

outcomes such as cardiac tamponade, pericardiocentesis and surgical drainage occurred in <10% of our patients, and that almost all outcomes occurred during the first few days after pericardial effusion was diagnosed. We also found that although few patients had effusion-related outcomes, echocardiographically determined effusion size was a powerful predictor of outcome, and that right-sided chamber collapse and IVC plethora with blunted response to respiration added little if any additional prognostic information.

What conclusions can be obtained from these data? First, most patients with large effusions had either cardiac tamponade or drainage procedures during their hospitalizations. Because these patients are likely to have an effusion-related outcome while in the hospital, aggressive monitoring and early intervention are probably warranted in this group.

Second, patients with small effusions seldom progress to cardiac tamponade or require drainage procedures. The only patient with a small effusion who developed cardiac tamponade had coronary artery bypass surgery after the index echocardiogram. This surgery resulted in a retrocardiac hematoma that caused tamponade. Furthermore, the 4 drainage procedures performed in patients with small effusions were done incidentally (e.g., opening of the pericardium during surgery for valve replacement). Thus, the paucity of effusion-related outcomes in patients with small effusions suggests that unless a patient's clinical condition changes, serial echocardiograms to assess for change in effusion size are unlikely to be of value.

Third, because patients with moderate effusions have a small but significant number of adverse outcomes, follow-up echocardiograms in these patients are probably worthwhile. However, the 2 patients in this group with cardiac tamponade had myocardial perforations during accessory pathway ablation procedures. Since these patients were easily recognized clinically, an aggressive therapeutic approach should probably be reserved for patients with moderate effusions who demonstrate hemodynamic impairment. These 2 patients also underscore the importance of rate of fluid accumulation. Both patients had rapid development of tamponade in the setting of moderate effusions without right-sided chamber collapse. The absence of right-sided chamber collapse may have been due to a variety of causes (including aggressive fluid loading) and again suggests that the decision to intervene in patients with moderate effusions should be based on clinical rather than echocardiographic findings.

Finally, the data suggest that right ventricular collapse, right atrial collapse, and IVC plethora with blunted response to respiration may be less diagnostic of cardiac tamponade than previously thought. Cardiac tamponade was present in less than half of our patients with right ventricular collapse (6 of 13) and in less than a quarter of those with right atrial collapse (3 of 21). Although the specificities and negative predictive values of these signs were ≥70%, the low positive predictive values (<50%) suggest that in most cases, these signs were false positive findings.

These findings are not incompatible with those of previous studies documenting impressive sensitivities, specificities and predictive values for echocardiographic signs of cardiac tamponade.[7–16] Most previous studies excluded patients with small pericardial effusions and had study cohorts in which a large number of patients had cardiac tamponade. Although these types of studies can reliably estimate sensitivity and specificity, predictive values are strongly influenced by the prevalence of disease in the population.[17] Because our study investigated the echocardiographic signs of tamponade in a more complete spectrum of patients than did previous studies, the positive and negative predictive values we obtained may be more generalizable to average patient populations.

Two potential limitations should be mentioned. First, our study population was restricted to hospitalized patients with pericardial effusion. These patients are likely to have a different clinical profile than outpatients with pericardial effusion, and consequently, the results may not be applicable to those with pericardial effusion who are observed in outpatient settings.

Second, the fact that a patient has pericardiocentesis or surgical drainage while in the hospital does not necessarily mean that the procedure is required. Knowledge of echocardiographic findings undoubtedly influences the decision to intervene. However, our findings were similar whether we used cardiac tamponade or a combined end point for analysis, and also whether we analyzed all 187 patients or restricted our analysis to the 50 high-risk patients with moderate and large effusions. Because of the consistency of the results, we believe that they are both sound and clinically relevant.

In conclusion, our results suggest that echocardiographically determined effusion size is a powerful predictor of outcome in hospitalized patients with pericardial effusion, and that right-sided chamber collapse and IVC plethora with blunted response to respiration add little if any additional prognostic information. Based on these results, we believe that hospitalized patients with large pericardial effusions merit aggressive monitoring and early intervention, those with moderate effusions should have follow-up echocardiograms, and those with small effusions only need follow-up echocardiograms if there is a change in their clinical condition.

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A New Method for Evaluating Lung Uptake of Thallium-201 During Stress Myocardial Scintigraphy

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A novel, multipurpose device has been designed that allows thallium activity to be continuously studied from a given lung area at rest and at peak exercise. The information gained from this technique proves to be relevant and reliable because lung thallium activity is displayed in real time and the interpretation of thallium distribution is not based on qualitative or quantitative comparison with that in the myocardium or mediastinum. The time-activity curves obtained in our study group are reported and the relation of peak activity to plateau activity (peak/plateau ratio) is proposed as an index that is easy to obtain for identifying patients with normal and impaired left ventricular function.

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Myocardial imaging with thallium is a noninvasive technique that has been increasingly used for visualizing the regional distribution of myocardial blood flow in patients with coronary artery disease[1] but has never been considered helpful in identifying patients with heart failure. The intriguing observation has also been made that some patients with exercise-induced left ventricular dysfunction have a greatly increased pulmonary uptake of thallium-201 compared with healthy subjects.[2] Based on subsequent human and animal studies that also used gated blood pool imaging,[3–10] the intensity of lung activity has been assumed and later demonstrated to be a marker for abnormal left ventricular function in the absence of left atrial hypertension and chronic pulmonary disease. The sensitivity of this scintigraphic method is rather poor when thallium lung uptake and exercise-induced changes in radionuclide-determined pulmonary blood volume are compared within the same group of patients with coronary artery disease. The reduced sensitivity of the technique has been attributed to: (1) the gradual decrease in lung thallium activity from its maximal value at peak exercise (the requirement for gamma camera positioning and the significant operator interaction make this delay critical and unavoidable); and (2) the currently available standards for interpreting thallium lung uptake images based on qualitative or quantitative comparison with that of the myocardium, the mediastinum and/or a given lung area in the initial anterior image. Even this latter approach has some limitations because the 2 lung areas where counting is done may differ and because once again there is a time lag between the intravenous injection of thallium and the onset of imaging.

This study describes a new device that overcomes limitations of the conventional techniques. We also report the preliminary results obtained with this new technique for detecting thallium lung uptake.

METHODS

A special, multipurpose device was needed that allowed the continuous recording of thallium activity from a given lung volume at peak exercise while the tracer was injected intravenously and the patient was exercising on either a motor-driven treadmill or a bicycle ergometer. To provide such conditions, a special device was created at the Department of Nuclear Engineering of Politecnico in Milan. Basically, the system operates with a series of 4 or, if required, 8 multicrystal scintillation detectors with external dimensions of 27 ×

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35 mm (Quartz & Silice Holland, B.V., the Netherlands). Each detector contained a thallium-drifted cesium iodide (10 × 10 × 10 mm^3) crystal, a photodiode and a preamplifier. Each scintillation crystal detector was then connected to a digital-to-analog conversion amplifier. The signal was put into an analyzer that recorded only signals within a fixed energy window (the upper and lower limit cut-off for thallium is 135 to 167 keV). The amplified and filtered signal was monitored automatically at 1-second counts in continuous succession. This output was acquired by a computer that allowed the counting to be saved on a spreadsheet and the corresponding time-activity curves to be displayed in real time on a monitor. The recorded data could be selected for printing and for quantitative analysis according to standard statistical and mathematic procedures. Dedicated software allowed both data management and changes in the integration time. Each detector was placed inside a lead container that served as a 3-mm-thick shield and that also carried a cylindrical collimator (4 mm in diameter × 6 mm in height). The miniature lightweight scintillation probes were firmly fixed to the patient's chest and held comfortably in place by simple adhesive tape. In general, 4 detectors were used. One detector was placed on the arm through which thallium was to be injected. Its function was to record the beginning, the end and the time course of the intravenous injection of the tracer. The remaining 3 detectors were placed along the midclavicular line, on the anterior aspect of the right hemithorax; one of them was fixed just below the clavicle to detect the passage of thallium bolus through the veins of the upper chest and to record the delayed radioisotope activity from the upper part of the right lung. Another detector was placed in the fourth right intercostal space to record thallium activity from the central portion of the ipsilateral lung. To make sure that only lung activity was recorded, interference from myocardial activity was avoided by adequate angulation and collimation of the detector. The last detector was placed in the twelfth right intercostal space to record liver uptake.

Our study group underwent rest electrocardiography, standard chest roentgenography, echocardiography and exercise-thallium scintigraphy. The patients exercised upright on a bicycle ergometer according to the widely used Bruce protocol. Electrocardiographic lead II was monitored continuously during exercise, and leads II, III, aVF and V_5 were monitored at 2- to 3-minute intervals during exercise. Arm cuff blood pressure was measured every minute during the bicycle ergometer test and for 2 minutes in the recovery time. Lung activity was recorded continuously from a given lung volume at peak exercise, in the 30 seconds before the anticipated intravenous injection of thallium and in the 10 minutes after administration of the tracer. The counting was integrated at 1-second intervals. The patient was invited to exercise for 90 additional seconds.

Validation of the technique: The width of the shield, the diameter and the height of the collimator were assessed in vitro by positioning the scintillation probe over a test plastic bag containing either saline solution or a solution with different, known thallium-201 concentrations. This test bag was surrounded by 3 other plastic bags whose aim was to simulate the contribution of radioactivity emanating from the veins of the upper thorax, the heart and the liver, respectively. The changes in counting rates were related to the thallium-201 concentration inside the test bag.

RESULTS

Our technique was tested in 10 subjects (5 men and 5 women, mean age 54 ± 6 years). In all cases the curves were similar in that they consisted of a swift upstroke that culminated in a dome-shaped peak. The curves then declined and ended in a plateau. However, a striking qualitative difference in the curves was noted when plateau activity was compared with peak activity. To exemplify this difference we show the pathognomonic time-activity curves obtained from the central portion of the right lung in 4 of our patients. In the first 2 subjects (Table I), the plateau amplitude was low (Figure 1) but in the last 2 subjects (Table I) the plateau amplitude was clearly exaggerated in height relative to the peak (Figure 2). Figure 1 (top) is from a 58-year-old healthy subject, and Figure 1 (bottom) is from a 48-year-old, asymptomatic patient who had an uncomplicated inferior myocardial infarction and who had shown neither ST-segment ischemic displacements nor reversible defects in myocardial perfusion on exercise testing. The size of the heart, left ventricular internal dimensions and ejection fraction were normal as assessed from the chest film and from the echocardiogram. The last 2 time-activity curves were from 2 patients with signs of diffuse ischemic lesions. The former (Figure 2, bottom) was a 56-year-old subject with a history of previous myocardial infarction. The ventricular septum, the apex, and the anterolateral and inferior walls in this patient were akinetic as documented by both myocardial scintigraphy and echocardiography. This examination also demonstrated concomitant mitral regurgitation and a depressed resting ejection fraction that averaged 40%. The patient was asymptomatic and showed neither ST-segment shifts nor reversible perfusion defects while performing the stress test and undergoing stress myocardial scintigraphy, respectively. Fig. 2 (bottom) is from a 60-year-old patient affected with essential hypertension and angina pectoris that was brought on by minimal exertion. The stress test documented an asymptomatic ST-segment depression in the inferior and anterolateral leads. Myocardial scintigraphy demonstrated a reversible defect in the anterior and lateral cardiac walls as well as in the apical and septal segments.

The peak to plateau relation was also quantitated from the mean of the first 10 highest values at peak and from the mean of the 10 values acquired on the plateau 60 to 70 seconds at the onset of the time-activity curve. The peak to plateau ratio was then computed and reported in descending order (Table I) together with the single mean ± SD of the peak and plateau values, the clinical and laboratory features of our patients. The peak/plateau ratio was higher in the former 2 than in the latter 2 patients who indeed had more severe signs of myocardial dysfunction.

TABLE I Clinical and Laboratory Features of Study Patients

Pt.	Age (yr) & Sex	Peak (cps)	SD	Plateau (cps)	SD	A/B Ratio	History	Exercise Testing	Scintigraphy
1	58 M	156.00	20.16	42.50	5.81	3.67	Normal	No changes	Normal
2	48 M	84.40	28.39	38.80	5.15	2.74	Inferior infarct	No changes	Fixed inferior defect
3	50 F	176.80	51.84	65.40	9.32	2.70	Non-Q Infarct	No changes	Normal
4	43 M	129.20	19.77	54.40	5.58	2.37	Inferior infarct	No changes	Fixed inferior defect
5	63 F	130.90	28.39	57.20	6.67	2.28	Angina pectoris, arterial hypertension and diabetes mellitus	Inferior ischemia	Reversible defect in the apex, inferocapical and inferoseptal segment
6	52 F	105.90	14.13	56.50	7.04	1.87	Angina pectoris and arterial hypertension	Anterolateral ischemia	Reversible defects in the anterocapical, basal septum and inferocapital segment
7	56 F	94.60	20.03	53.10	6.71	1.78	Anterior infarct and diabetes mellitus	Anterolateral ischemia	Fixed defects in the anterior wall and in the apicoseptal segments; reversible inferior
8	54 F	123.20	17.78	70.09	6.38	1.76	Anterior infarct and aneurysm	No changes	Fixed defects in the anteroapical, inferior, basal septal and inferoseptal segment
9	56 M	117.80	8.53	67.60	5.01	1.74	Anterior infarct	No changes	Fixed defect in the anteroapical, basal septal, inferoseptal and inferobasal segment
10	60 M	60.20	10.68	37.50	8.04	1.60	Angina pectoris	Anterolateral and inferior ischemia	Reversible defects in the apex, septum, anterior and lateral walls

Values are mean ± SD of peak and plateau values and peak/plateau (A/B) ratio.
cps = counts per second.

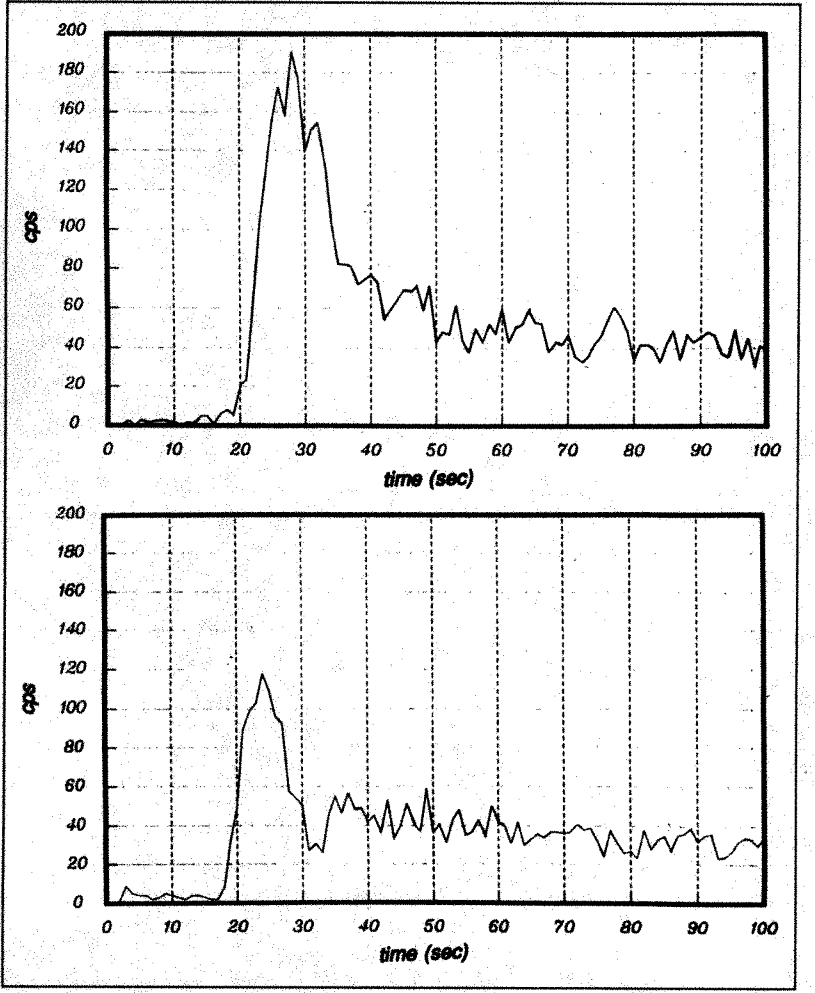

FIGURE 1. Time-activity curves from the central portion of the right lung in subjects with normal left ventricular function. In both cases plateau activity proved to be low relative to peak activity. cps = counts per second.

DISCUSSION

The new device developed in our laboratory allowed thallium activity to be continuously recorded from a given lung area both at rest and while the patient was undergoing upright bicycle exercise. Because of its miniaturized lightweight detectors, our device could not even interfere with a simultaneous recording of hemodynamic variables and of myocardial imaging with either invasive or noninvasive methods, respectively. In addition, the recording of thallium lung activity was not interfered with by the radioactivity from other areas because of the adequate inclination and collimation allowed for by the small detectors. In addition, relevant information was gained in a very short time by analysis of thallium lung uptake at peak exercise. In contrast to alternative thallium techniques, our device offered the unique advantages of supplying adequate time-activity curves with the use of standard doses of thallium and of detecting maximal effects of peak exercise on pulmonary circulation when thallium washout had not yet taken place. Because transudation of fluid into the pulmonary interstitial space and increased thallium lung uptake were known to correlate with exercise-induced elevations in left ventricular filling pressure,[11-14] left ventricular dysfunction could easily be recognized by thallium distribution in the lung, provided chronic pulmonary disease and other causes of increased venous pulmonary pressure had been excluded (i.e., mitral valve disease).

The contour of the time-activity curves was similar in all patients studied and consisted of a swift upstroke that culminated in a dome-shaped peak. The curve then declined and ended in a plateau. The early increase in radioactivity and the initial phase of the plateau were thought to be due to the passage of thallium bolus through the pulmonary vessels and to the amount of thallium filtered in the pulmonary interstitium, respectively. The hypothesis that the initial phase of the plateau could be taken as a reliable index of thallium extraction fraction was supported by the observation that the short time interval between thallium injection and the onset of imaging could not reasonably interfere with the removal of the tracer from the lung. The time-activity curves obtained in our study group could be compared when the initial phase of the plateau was assumed to represent thallium extraction fraction and when the continuous recording of thallium activity in each subject was thought to take place from the same lung area and under the same conditions. The peak/plateau ratio was thus proposed as an easy-to-obtain index of a mutual

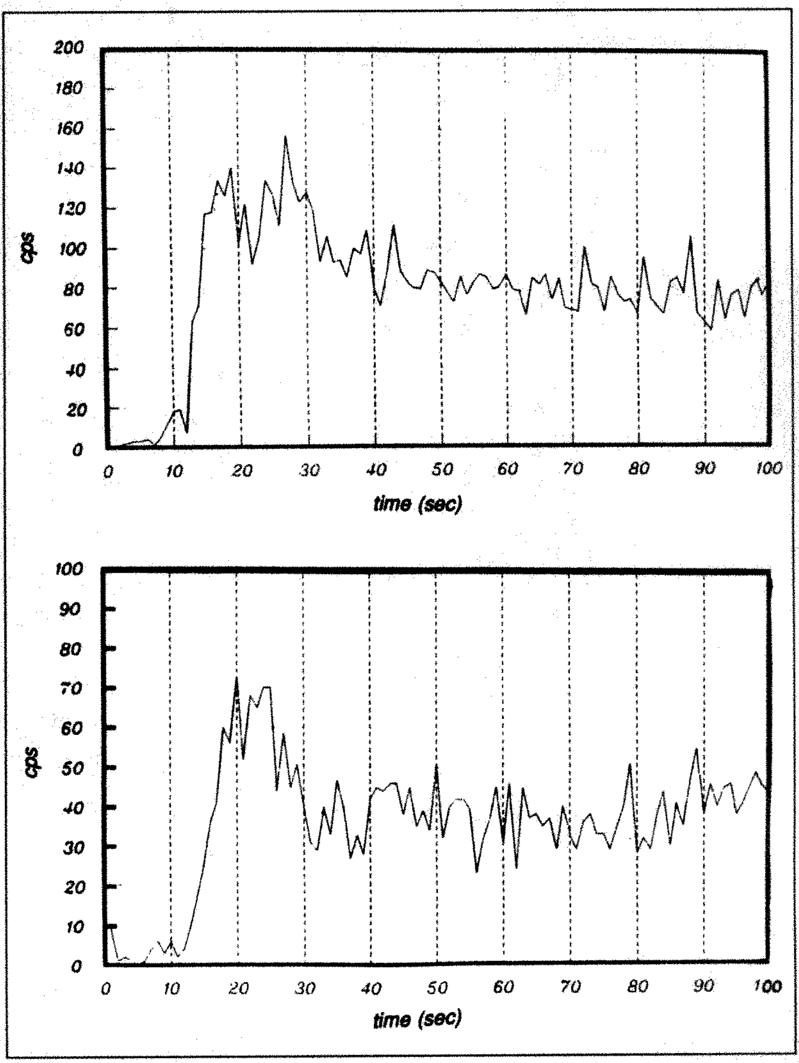

FIGURE 2. Time-activity curves from the central portion of the right lung in 2 patients with impaired left ventricular function. Note that plateau amplitude was abnormally high relative to peak activity. cps = counts per second.

relation between the measures obtained at peak and in the initial phase of the plateau, respectively. Computation of the peak/plateau ratio allowed the random variables operating in each patient, namely the geometric and attenuation factors, to be cancelled out and therefore to make patient comparison possible. Analysis by this criterion showed that patients with impaired left ventricular function had an abnormally low peak/plateau ratio as opposed to subjects with normal left ventricular function. In this regard, our data are consistent with previous studies which suggested that increased thallium uptake by the lungs is useful for detecting left ventricular dysfunction during stress in patients with chronic pulmonary disease and in the absence of mitral valve disease. Our system is based on the use of miniaturized scintillation probes that allow thallium lung uptake activity to be recorded very easily and quickly from the same lung area at peak exercise. Our system provides a reliable, low-cost, noninvasive means of detecting left ventricular dysfunction, and it precludes neither a simultaneous recording of hemodynamic variables nor the performance of myocardial scintigraphy. We think that the present results may encourage further investigation, especially in a larger number of patients with varying degrees of left ventricular dysfunction induced by exercise.

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Prevalence of Coronary Artery Disease in Asian Indians

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Asian Indians constitute approximately one fifth of humanity. Eleven million of these Asian Indians live outside India, including about one million in the United States. Of these, 25,000 are physicians and constitute 5% of all physicians practicing in the United States. Coronary artery disease (CAD) incidence and mortality have been reported to be unusually high among Asian Indians.[1-16] Such reports come from Singapore, Uganda, South Africa, Fiji, Trinidad, Mauritius and United Kingdom. Estimates of the excess risk compared to the indigenous population range from 2.5 to 5 for myocardial infarction and 1.5 to 3 for CAD mortality[1,16-18] (Table I). This review is an attempt to familiarize cardiologists with the magnitude and severity of CAD, differences in the prevalence of risk factors, differences in treatment of risk factors, and possible differences in approach to dietary recommendations between Asian Indians and other racial groups in the United States.

Prevalence of coronary artery disease in Indians in the United Kingdom and India: Balarajan[9] analyzed the mortality data for England and Wales for 1970 to 1972 and 1979 to 1983 to determine changes in CAD mortality among various immigrant groups. CAD mortality during the period of 1970 to 1983 generally reflected the rates reported in the country of origin of various migrant groups.[1,9] During this period England and Wales had one of the highest rates of CAD mortality, having experienced only a minimal decline (5% in men and 1% in women) overall. In this study immigrants from the United States showed a 23% decline in CAD mortality in men and 36% decline in women. This is similar to the 28% overall decline in CAD mortality from 1976 to 1986 in the United States.[19] In sharp contrast, those born in the Indian subcontinent, despite having had the highest death rates from CAD in the 1970 to 1972 survey, experienced an increase of 6% in men and 13% in women. This resulted in an excess CAD mortality of 36% in Asian Indian men and 46% in Asian Indian women during 1979 to 1983 compared with the overall rates in England and Wales (Table II).

Although most immigrants tend to be generally healthier than the population they left behind, the CAD mortality in the first generation of immigrants tends to be intermediate between that of their country of origin and the land of adoption. Within 1 or 2 generations, the pattern of mortality tends toward that of the adopted country as shown by the westernized Japanese-Americans.[17,20] However, the CAD mortality among Asian Indian immigrants continues to diverge from their compatriots of other ethnic origin.[8,9,14]

Although the prevalence of CAD in India was reported to be comparable to the United States, in the 1960s,[21] when the United States had the second highest CAD mortality in the world, big geographic differences between different parts of India were present. CAD was 7 times more common in the Southern states of India compared with the Northern states.[22] There are no current population-based data on CAD incidence, prevalence or mortality in India.[1] Although there are numerous anecdotal experiences of increasing incidence, prevalence, prematurity, severity and mortality of CAD in both urban and rural India, there are no reports of a decline in CAD in India, unlike the marked reduction in the incidence of CAD in several Western nations.

Early and extensive atherosclerosis in Asian Indians: CAD among Asian Indians is often premature, severe, extensive and follows a malignant course. The first myocardial infarction is usually massive, resulting in higher rates of permanent disability and evaluation for heart transplant.[4,12,18] Quantitative analyses of coronary angiograms (34 Asian Indians and 68 whites) by Lowry et al[12] have shown more severe disease in Asian Indians than in whites. Lowry et al[12] recommended early investigation of Asian Indians because more of them were found to be unsuitable for coronary artery bypass surgery (59 vs 47%) because of the severity of disease. The need for early intervention was further supported by the fact that 25% of Asian Indians who were refused surgery died within a period of 19 months compared with 6% of the whites.[12] In a prospective comparison of 131 men (77 whites, 54 Asian Indians) admitted to a coronary care unit in the United Kingdom, the rate of a first myocardial infarction was 5 times higher among the Asian Indians than among the native English, after adjusting for the distribution of various ethnic groups in the area.[18] The age at myocardial infarction was lower in Asian Indians (50.2 years) than in white patients (55.5 years). The age-specific rates of myocardial infarction in Asian Indians was particularly marked in younger persons and was almost 10 times the rate observed in whites between the ages of 30 and 39 years. The size of myocardial infarction assessed by peak creatine kinase, or degree of ventricular dysfunction assessed by radionuclide and contrast ventriculography was significantly greater in Asian Indians. Asian Indians had >2 times the frequency of 3-vessel CAD (54 vs 21%) and substantially higher atheroma scores in arteries not associated with myocardial infarction (3.66 vs 1.97).

From the Coronary Artery Disease Among Indians Study, Woodridge, Illinois; the Clinical Trials Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute, Bethesda, Maryland; and the Division of Cardiology, University of Florida College of Medicine and Veterans Administration Medical Center, Gainesville, Florida. Manuscript received April 27, 1992; revised manuscript received and accepted June 5, 1992.

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TABLE I Coronary Artery Disease Mortality Among Overseas Asian Indians Compared with the Indigenous Population

	Period of Survey	Standardized Mortality* (no.)	Ref.
Singapore	1954–1957	400	2
South Africa—Women	1955–1957	149	5
Singapore	1957–1978	300	3
South Africa—Men	1968–1977	145	1
Fiji	1971–1980	300	6
Trinidad compared with Africans	1977–1984	260	7
Trinidad compared with mixed descent	1977–1984	820	7
London boroughs	1979–1983	150	13
England and Wales—women	1979–1983	146	9
England and Wales—men	1979–1983	136	9
England and Wales—men (age 20–29 years)	1979–1983	313	9

*Standard mortality in the reference indigenous population is 100.
Ref. = reference.

The relative excess in mortality in the United Kingdom among Asian Indian men, compared with overall rates in England and Wales, was greatest in young persons. For example, mortality from CAD was 2.1 times higher in Asian Indian men compared with Non-Indians between the ages of 30 to 39, and 3.1 times higher between the ages of 20 to 29.[9] These observations suggest that atherogenesis is accelerated in Asian Indians and leads to high rates of premature mortality and morbidity from CAD.[18]

Traditional risk factors: Examination of the 3 major risk factors (high serum total cholesterol, high blood pressure and cigarette smoking) has failed to explain the high incidence of CAD in Asian Indians.[1,7,8,14,23] Smoking is less frequent among Asian Indian men and unusual among Asian Indian women who live outside of India.[7,11,24,25] Blood pressure is generally lower in Asian Indians than in whites.[24,25] The total cholesterol level is also lower.[4,11,24,26] The only known major risk factor for CAD that appears to be more prevalent among Asian Indians is diabetes mellitus,[7,8,27–29] which also develops earlier in life.[8] The excess prevalence of diabetes mellitus varied in these studies and was 3.8 to 4.3 times more common, compared with whites in the United Kingdom.[28,29]

To determine the prevalence of CAD and its risk factors in Asian Indians who migrated to the United States, 1,456 adult Asian Indian physicians and their family members (spouses, children and parents) were recently surveyed as part of the Coronary Artery Disease Among Indians Study.[30] Subjects were drawn from attendees at national conventions. Blood was obtained for analyses of glucose and lipoproteins in 461 of these subjects. The prevalence of angiographically documented CAD (i.e., angina or myocardial infarction followed by coronary arteriography) was 3 times more common in Asian Indian men compared with clinically diagnosed cases among men (i.e., clinical diagnoses of angina or myocardial infarction) from the Framingham Offspring Study.[31] Although the prevalence among women appeared to be the same, the number of female subjects in the 2 groups was too low to make reliable comparisons. Asian Indians had significantly higher prevalence of diabetes mellitus, hypertriglyceridemia and lower serum levels of high-density lipoprotein (HDL), but lower prevalence of cigarette smoking, systemic hypertension, family history of premature CAD and obesity compared with the Framingham Offspring Study. There was no difference in the prevalence of elevated (>240 mg/dl) total cholesterol levels, elevated (>160 mg/dl) low-density lipoproteins (LDL) cholesterol levels, or a history of stroke and peripheral vascular disease between the groups.[30]

This pattern of higher prevalence of diabetes mellitus, low HDL and high triglyceride among Asian Indians in the United States without elevations in LDL or higher prevalence of cigarette smoking or systemic hypertension is consistent with reports from other countries.[1,7,11,26,28,32] Furthermore, this pattern contrasts sharply with the distribution of risk factors in whites, among whom higher levels of LDL, and higher preva-

TABLE II Change in Coronary Artery Disease Mortality in England and Wales Among Persons Aged 20 to 69 Years by Country of Birth from 1970 to 1972 and from 1979 to 1983

	Men			Women		
Country of Birth	1970–72 SMR	1979–83 SMR	% Change in SMR	1970–72 SMR	1979–83 SMR	% Change in SMR
Scotland	124	111	−10	124	119	−4
All Ireland	113	114	+1	122	120	−2
African Commonwealth	116	113	−3	78	97	+24
Old Commonwealth	110	91	−17	94	72	−23
Caribbean Commonwealth	49	45	−8	89	76	−15
West Europe	84	77	−8	87	81	−7
East Europe	111	112	+1	115	110	−4
Republic of South Africa	117	90	−23	115	73	−37
United States	112	86	−23	87	56	−36
India	128	136	+6	129	146	+13
All England and Wales	105	100	−5	101	100	−1

Adapted from Balarajan[9] and reproduced with permission.
SMR = standardized mortality ratios with England/Wales rates for 1979 to 1983 as the standard.

lence of hypertension and cigarette smoking have been implicated in the development of CAD. Obviously, factors other than the cigarettes-cholesterol-hypertension paradigm must be diligently explored in this population.

Low high-density lipoproteins — a powerful risk factor: Numerous epidemiologic studies from North America, Europe and Israel have conclusively demonstrated that an elevated level of HDL protects against CAD, and an abnormally low level of HDL increases the risk of CAD.[33-39] A low level of HDL is a powerful independent risk factor for the future risk of CAD, not only when total cholesterol is high, but also when total cholesterol is not elevated.[33-39] In the Physician's Health Study, myocardial infarction was 3.2 times more common in the subgroup of men with a total cholesterol of <212 mg/dl and HDL of <47 mg/dl compared to those with similar total cholesterol and HDL of >47 mg/dl.[34]

The analysis of the relation between HDL and the development of myocardial infarction in the Framingham Study has also shown similar results. After 12 years of follow-up, men with HDL of <52 mg/dl had a 60 to 70% excess of myocardial infarction compared with men whose HDL levels were higher. The effect of HDL was even stronger in women, in whom a sixfold excess of myocardial infarction was reported, with a decrease of HDL from >66 to <46 mg/dl.[38] Based on the Framingham data, optimal HDL levels should exceed 52 mg/dl for men and 66 mg/dl for women.[38]

Only 14% of the Asian Indian men and 5% of Asian Indian women had the optimal HDL in the Coronary Artery Disease Among Indians Study.[30] Mean HDL in Asian Indian men is on an average 5 mg/dl lower than in white men, and 15 mg/dl lower than in black men and Japanese men. The gap in HDL levels appears to be even wider in Asian Indian women compared with women of other ethnic groups.[30]

Triglycerides, atherogenic lipoprotein and lipoprotein (a): Austin et al[40] recently described an atherogenic lipoprotein phenotype B characterized by moderate hypertriglyceridemia, a high proportion of small dense LDL, a high level of apolipoprotein B, and a low level of apolipoprotein A1 and HDL, especially HDL-2 which can be inherited as a single gene trait. The small, dense LDL particle appears to carry a threefold risk of CAD regardless of the absolute level of LDL. Atherogenic phenotype B can be differentiated from benign phenotype A by simple measurements of triglycerides and HDL. A triglyceride value of 95 mg/dl discriminates the 2 phenotypes in 83% of cases, whereas an HDL value of 39 mg/dl separates the 2 groups in 72% of cases.

The prevalence of this atherogenic phenotype is 25% in whites. When a triglyceride level of >95 mg/dl was used, 75% of Asian Indian men in the Coronary Artery Disease Among Indians Study demonstrated this phenotype.[30] Although the role of high triglycerides as an independent factor in the development of CAD remains controversial,[37,41] the data from several prospective studies suggest that triglycerides are probably an important risk factor.[42,43] Hypertriglyceridemia is often associated with increased plasminogen activator inhibitor levels and impaired fibrinolysis.[44] It is possible that elevated triglyceride and low HDL may be very important risk factors among Asian Indians and perhaps as important as LDL in whites and hypertension among blacks.

Recent studies indicate that elevated lipoprotein (a) levels are strong predictors of CAD.[45,46] Lipoprotein (a) levels may be related to both atherogenesis and thrombogenesis and may be a key link between lipids and thrombosis, because its sugar-rich portion competes with plasminogen and the modified apolipoprotein B moeity is actively taken up by the foam cells. The levels of lipoprotein (a) were found to be 3 times higher in Asian Indians than in Chinese in Singapore.[45] This parallels the threefold excess mortality reported among Indians in Singapore compared with the Chinese.[1,3,45] The Coronary Artery Disease Among Indians Study has also demonstrated higher levels of lipoprotein (a) among Asian Indians in United States than among whites.[30]

Diabetes mellitus, hyperinsulinemia and abdominal obesity: McKeigue et al[28] studied the relation between anthropometric measurements and biochemical abnormalities in 1,515 Asian Indian men and 291 Asian Indian women and compared these data with a similar number of European and Afro-Caribbean men and women in the United Kingdom. Although there was no difference in body mass index between the groups, the Asian Indians showed a pronounced tendency for abdominal obesity evident by a higher waist-to-hip ratio. A 0.04 unit increase in waist-to-hip ratio in Asian Indian men (0.98 Asian vs 0.94 European) was associated with a fourfold increase in diabetes mellitus (20% among Asians vs 5% among Europeans) and twofold higher postglucose insulin levels (41 mU/ml in Asian Indians vs 19 mU/ml in Europeans) along with significantly high triglycerides and low HDL. In sharp contrast, Afro-Caribbeans who are known to have low CAD rates in the United Kingdom did not have abdominal obesity (waist-to-hip ratio 0.94 Afro-Caribbeans vs 0.94 Europeans) or hyperinsulinemia (22 mU/ml in Afro-Caribbeans vs 19 mU/ml in Europeans) despite a higher prevalence of diabetes mellitus similar to that in Asian Indians (15% in Afro-Caribbeans vs 20% in Asians).

These findings suggest that the etiology and consequences of non-insulin-dependent diabetes mellitus is different in blacks compared with Asian Indians. It is likely that high HDL levels in blacks may explain their lower CAD mortality compared with the Indians, despite a high prevalence of both diabetes and hypertension.[28]

Indian origin, insulin resistance and syndrome X: Hyperinsulinemia resulting from insulin resistance has been found to be a distinguishing feature and an independent predictor of CAD in men, both within and between populations in many prospective studies.[42,43,47,48] Higher levels of insulin after a glucose load have been reported in Asian Indians with increasing frequency.[24,26,28,47-51] Hyperinsulinemia is a marker of atherogenic pattern of risk factors and lipid profiles that is associated with the high rate of CAD in men in affluent societies. This has been called syndrome X by Reaven[52] or the deadly quartet by Kaplan.[53] It is often a precursor to diabetes and has been documented to antedate non-insulin-dependent diabetes mellitus by ≥ 8 years.[54] High triglyceride, low HDL, android obesity, glucose intolerance and predisposition to diabetes seen consistently among overseas Asian Indians constitute the hallmarks of this syndrome.[7,8,28]

Thus, a higher prevalence of insulin resistance syndrome appears to be the most plausible pathogenetic mechanism responsible for the metabolic and lipoprotein abnormalities resulting in high morbidity and mortality from CAD among Asian Indians.[7,8,9,16,24,28,55]

Dietary patterns among Asian Indians: There is considerable variation in the diet among Indians living inside or outside India, making it impossible to categorize the average Indian diet as high or low in fat. Even a vegetarian diet in India can be rich in saturated fats. Roberts[56] has called this "contaminated vegetarianism." Many vegetarian dishes are often cooked in clarified butter (ghee) and served with large amounts of cream. Furthermore, coconut oil (92% saturated fat) and palm kernel oil (86% saturated fat) are commonly used in cooking vegetables and other foods in certain regions in India. The average Indian diet in the United Kingdom and probably in the United States and India is high in carbohydrate, vegetable fiber and polyunsaturated fat, and low in cholesterol, saturated fat and omega-3 fatty acids of marine origin. Alcohol consumption is also low.[1,11,26] The low HDL and high triglyceride seen so frequently among Asian Indians[1,8,28,32] is surprisingly not associated with general obesity[1,26,28,30] and is also consistent with the reportedly low fat, high carbohydrate diet among them.[26,57]

A similar observation was made in the Coronary Artery Disease Among Indians Study, which indicated that the Asian Indians in the survey consumed a diet very similar to the step 1 diet of the American Heart Association. There were no significant differences in the serum levels of total cholesterol, triglyceride, LDL, HDL, apolipoprotein A1, apolipoprotein B and CAD between vegetarian and nonvegetarian Asian Indians.[30] This interesting phenomenon is probably due to smaller servings and infrequent consumption of meat by the nonvegetarians.[30]

Relevance of National Cholesterol Education Program Guidelines to Asian Indians: The current National Cholesterol Education Program guidelines focus primarily on the use of total cholesterol measurements as a means of identifying high-risk persons. They focus on reducing the LDL levels and recommend lipoprotein analysis only when total cholesterol is >240 mg/dl or when total cholesterol is between 200 and 239 mg/dl among persons with CAD or 2 other risk factors.[58] Bush and Riedel[59] recently reported that 66% of persons who are at high risk because of low HDL (<35 mg/dl) will not be identified by applying the National Cholesterol Education Program algorithm to the subjects in the Lipid Research Clinic Prevalence Study. An even higher percentage of Asian Indians who may be at high risk because of low HDL will not be identified using the National Cholesterol Education Program guidelines.[30] Thus, it seems likely that strict adherence to the algorithms proposed by National Cholesterol Education Program would miss the overwhelming majority of high-risk Indians. Therefore, screening lipid tests in Asian Indians should routinely include measurement of lipoproteins.[55]

Conclusions and implications: Asian Indians have one of the highest rates of CAD of any ethnic group. This excess is not chiefly due to a high fat diet or high serum cholesterol levels but probably due to abnormalities of glucose and triglyceride metabolism, insulin resistance and low HDL. The role of genetic factors mediated through apolipoprotein A1, apolipoprotein B, lipoprotein (a) and plasminogen activator inhibitor deserves further scrutiny. Given the difference in risk factors, the approach to the prevention of CAD in Asian Indians may also differ from that used in whites and blacks.

Measurements to lower LDL by a low-fat, high carbohydrate diet are unlikely to benefit such a population which traditionally consumes a high carbohydrate diet and whose major metabolic abnormality is low HDL with high triglycerides. Unfortunately, a low-fat, high carbohydrate diet may accentuate the metabolic abnormalities in this population.[60,61] In such persons preventive strategies should focus less on reduction of dietary cholesterol and saturated fats, and more on reducing triglycerides and raising HDL by a combination of regular exercise, weight reduction and decreased caloric and carbohydrate consumption. These recommendations, however, are logical, but not a proven fact.

Since there are no unique diets or medications that can raise HDL, the best dietary approach would be to improve the total cholesterol or LDL cholesterol to HDL ratio by partial substitution of monounsaturated fats for carbohydrates.[60–63] If lipid-lowering drugs are to be used, agents that increase HDL and decrease triglycerides should be considered. Future research should be focused on further elucidating the precise nature and etiology of the disturbances in glucose and lipid metabolism in this population.

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Usefulness of Accelerated Diastolic Reversed Flow Along the Left Ventricular Posterior Wall in Aortic Regurgitation for Estimating Left Ventricular Function

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Timely indication of surgical correction of aortic regurgitation (AR) depends on precise evaluation of left ventricular (LV) function. However, it may still be difficult to accurately predict surgical outcome with only currently available indexes of LV function. We undertook this study to obtain a novel index of LV function from altered LV fluid dynamics in patients with AR. AR flow is expected to cause definitive changes in intraventricular flow distributions. The degree of such changes may be mainly determined by the severity of regurgitation but variously affected by chamber size, diastolic property and filling pressure of the left ventricle. Therefore, our hypothesis is that the changes in the intraventricular fluid dynamics reflect LV function in patients with similar degrees of AR. We tested this hypothesis in patients with severe AR using the Doppler ultrasound technique and obtained a novel index for estimating LV function.

We prospectively studied 30 patients, 21 men and 9 women (mean age 53 years [range 25 to 86]) with severe AR undergoing routine echocardiography at Keio University Hospital. Eleven normal subjects (mean age 52 years [range 35 to 69]) without any cardiac abnormalities were selected as the control group. Only patients with technically good quality studies were included. The severity of AR was evaluated by Doppler color flow imaging, and only patients with a regurgitant flow transmitting over the papillary muscle level were selected. Patients with atrial fibrillation or coexisting mitral stenosis, or both, were excluded because of an abnormal mitral flow pattern irrespective of LV function. Seven patients with AR whose regurgitant flow was directed toward the LV posterior base instead of apex were also excluded beforehand because of the lack of diastolic reversed flow along the LV posterior wall.

All patients were studied at rest in the left lateral decubitus position with a Hewlett-Packard echocardiographic instrument (77030A Ultrasound System). Pulsed-wave Doppler signals were obtained from the apical long-axis view using a 2.5 MHz transducer. Mitral flow signals were sampled at the level of the tips of the mitral leaflets. Diastolic reversed flow signals were sampled at the center of the blue color signals representing that flow (Figure 1). If there was no visible diastolic reversed flow signals, we attempted to detect Doppler signals of diastolic reversed flow between the posterior mitral leaflet and posterobasal wall at the level of the tips of the mitral leaflets, where diastolic reversed flow is supposed to be present. Diastolic reversed flow signals were considered present if well enveloped, biphasic and with a velocity of >0.2 m/s.

Statistical significance of a difference of 2 means were determined by Student's t *test. Statistical correlation between acceleration of diastolic reversed flow and percent fractional shortening or LV end-systolic dimension were obtained using linear or nonlinear regression analysis.*

In all patients with severe AR, diastolic reversed flow signals could be detected using the pulsed-wave Doppler method, except for the particular patients described above. In the control group, diastolic reversed flow signals could not be detected in 2 patients. These 2 patients were excluded from statistical analysis.

Diastolic reversed flow signals were biphasic and were composed of 2 different signals similar to those observed in mitral flow signals. Each signal corresponding to E wave (rapid filling) or A wave (atrial contrac-

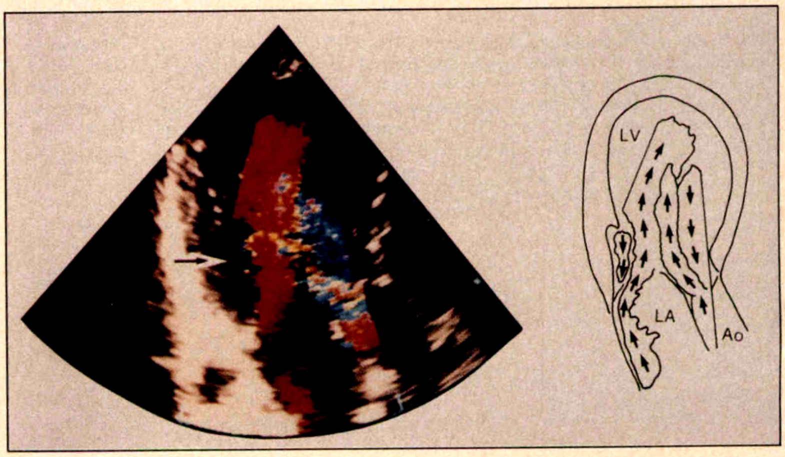

**FIGURE 1. Color Doppler imaging of diastolic flow in the left ventricle (LV) of patients with aortic regurgitation obtained from apical long-axis view *(left)*, and schematic *(right)*. A *blue color flow (arrow)* represents diastolic reversed flow along the left ventricular posterior wall.
Ao = aorta; LA = left atrium.**

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tion) in mitral flow signals were termed E' wave or A' wave (Figure 2). Each wave of diastolic reversed flow signals followed the corresponding wave of mitral flow signals with a slight time delay (30 to 90 ms). The mean peak velocities of each wave, including those of mitral flow, are listed in Table I.

The peak velocity ratio of diastolic reversed and mitral flows for each corresponding component was compared between the patient and control groups (Figure 3). In the patient group, the peak velocity ratio of E' and E waves (E'/E) was significantly higher than those in the control group, indicating that diastolic reversed flow is accelerated during the rapid filling phase. E'/E was roughly and linearly correlated with both percent fractional shortening and LV end-systolic dimension ($r = -0.49$ [$p < 0.01$] and 0.48 [$p < 0.01$], respectively). To eliminate inaccuracy due to technical failure in detecting peak flow velocity of E' and E waves resulting from inappropriate sampling position, we used the ratio of E'/E and A'/A (E'A/EA') as an index of altered fluid dynamics in the left ventricle, which we called DRFp-index. The DRFp-index correlated better with both percent fractional shortening and LV end-systolic dimension than E'/E (Figure 4). Furthermore, the index showed a relative constancy in the normal range of percent fractional shortening and LV end-systolic dimension; however, the index showed a progressive increase in accordance with progression of LV dysfunction.

TABLE I Mean Peak Wave Velocities of Mitral Flow and Diastolic Reversed Flow

Velocities (cm/s)	Control Group (n = 9)	Patient Group (n = 30)
E-wave velocity	71 ± 14	59 ± 19
A-wave velocity	69 ± 18	66 ± 18
E'-wave velocity	50 ± 18	53 ± 12
A'-wave velocity	50 ± 16	52 ± 16

All values are expressed as mean ± SD.

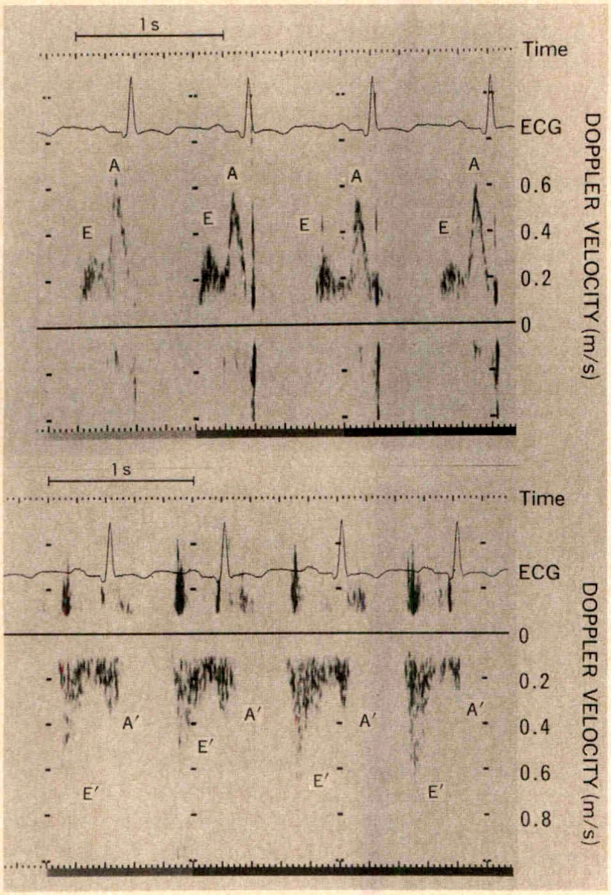

FIGURE 2. Pulsed-wave Doppler recordings of mitral flow *(upper tracing)* and diastolic reversed flow *(lower tracing)* in a patient with aortic regurgitation. Paper speed was 50 mm/min. The E'- and A'-wave signals are well-defined and follow identifiable E- and A-wave signals. ECG = electrocardiogram.

In the present study, we demonstrated an acceleration of diastolic reversed flow as altered fluid dynamics in the left ventricle of patients with AR. The energy source of the acceleration of diastolic reversed flow is expected to be supplied by the regurgitant flow energy, because the acceleration of diastolic reversed flow is likely to be caused by a driving force of regurgitant flow turning up at the LV apex. Therefore, the degree of the acceleration of diastolic reversed flow seems to be determined by the initial potential energy of regurgitant flow and the energy absorbing capacity of the left ventricle. The latter consists of chamber size, ventricular relaxation, chamber stiffness and filling pressure of the left ventricle. We therefore hypothesized that changes in intraventricular flow dynamics reflect LV function in patients with similar degrees of AR and proved the hypothesis in patients with severe AR.

We used the ratio of E'/E and A'/A, the DRFp-index, as an index of altered fluid dynamics in the left ventricle. This index may operate on the combining effects of the 4 variables that determine the energy-absorbing capacity of the left ventricle. Slowed ventricular relaxation and increased chamber stiffness decreases the energy absorbing capacity of the left ventricle and may facilitate the acceleration of diastolic reversed flow. On the other hand, chamber dilatation and elevated filling pressure increase the energy-absorbing capacity of the left ventricle and may impede the acceleration of diastolic reversed flow. Although chamber stiffness is a function of

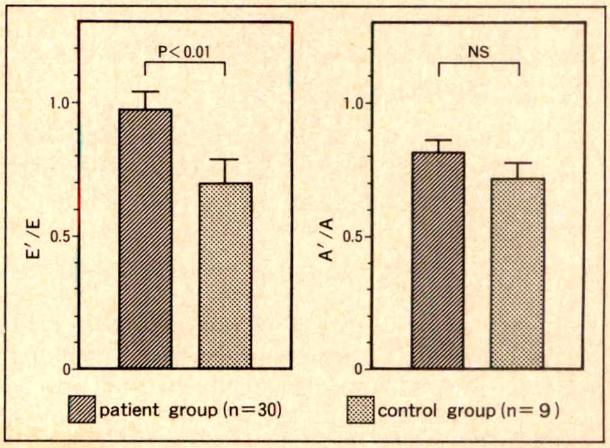

FIGURE 3. Comparison of the peak velocity ratio of each corresponding component of diastolic reversed flow and mitral flow between patient and control groups. All values are expressed as mean ± SEM.

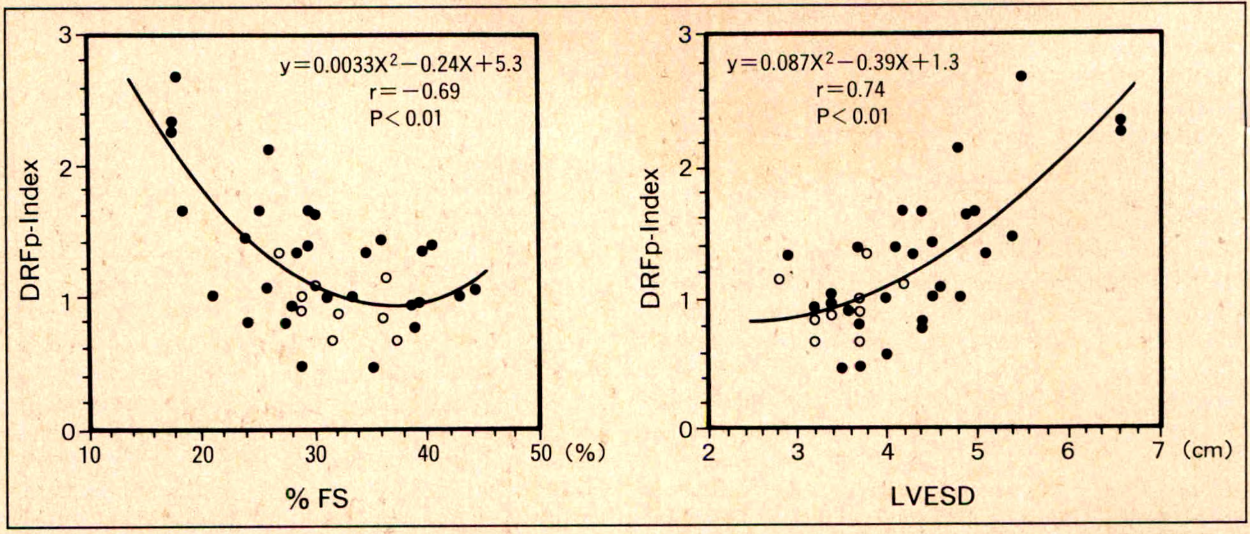

FIGURE 4. Relation between percent fractional shortening (FS) *(left panel)* or left ventricular end-systolic dimension (LVESD) *(right panel)* and DRFp-index. The values plotted are of the patient *(closed circles)* and control *(open circles)* groups.

filling pressure in the acute phase of volume overloading, chronic volume overloading causes slowed relaxation,[1] increased chamber stiffness[2,3] and chamber dilatation with little elevation of filling pressure[4] as a result of eccentric hypertrophy. The initiation of a significant elevation of filling pressure may represent a transition from hypertrophied myocardium to failing myocardium in patients with chronic AR. The net effect of slowed relaxation, increased chamber stiffness and chamber dilation is an acceleration of diastolic reversed flow, judging from the results of the present study. In this case, E' and A' waves may be accelerated in a similar degree. However, when an elevation in filling pressure supervenes as a result of the initiation of myocardial failure, the acceleration of diastolic reversed flow, especially that of the later component of diastolic reversed flow, may be impeded. As a result of the interference of the acceleration of A' wave, the acceleration of E' wave may become dominant, which results in an increase in the ratio of E'/E and A'/A, the DRFp-index. This may explain the characteristic response of the DRFp-index to progression of LV dysfunction.

In this study, we did not demonstrate superiority of the DRFp-index to other parameters to estimate LV function. It should be clear only when long-term follow-up of patients with AR is done using this index. However, this index derives not from ventricular mechanics but from ventricular fluid dynamics. Changes in myocardial function directly influence ventricular fluid dynamics without any intervention. Any trivial changes in LV function would be reflected better and more promptly on fluid dynamics than on ventricular mechanics. Therefore, we believe that the DRFp-index may become a useful and sensitive parameter for estimating LV function in patients with AR.

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Assessment of Aortic Valve Area in Aortic Stenosis by Magnetic Resonance Imaging

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The ultimate determinant of the clinical significance of valvular aortic stenosis (AS) is the systolic aortic valve orifice area (AVA). AVA can be quantified either at cardiac catheterization[1] or noninvasively using transthoracic Doppler echocardiography and the continuity equation.[2] For technical reasons, the Doppler interrogation is not always successful, however, and a substitute noninvasive method for AVA determination would be welcome. Ultrafast computed tomography has shown some promise in this respect,[3] and the present report describes our initial experience with the use of magnetic resonance imaging (MRI) to directly visualize and quantify the systolic aortic valve orifice.

We studied 48 patients, 25 men and 23 women aged 41 to 78 years (mean 63). They underwent cardiac cathe-

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terization between March 1990 and April 1991 at our institution because of AS with or without suspicion of coexistent coronary artery disease. They were consecutive patients with AS except that those with emergency catheterization, overt congestive heart failure or signs of more than minute aortic regurgitation were excluded. All were symptomatic with effort dyspnea or chest pain. Except for 2 patients, all were in sinus rhythm. The study protocol, accepted by the institutional ethical committee, consisted of (1) left- and right-sided cardiac catheterization with coronary angiography, aortic root cineangiography and an optional left ventricular cineangiography; (2) a combined 2-dimensional, M-mode and Doppler echocardiography; (3) MRI study of the heart; and (4) a thallium-201 exercise test (data not included in this report). The MRI and Doppler studies were performed 1 day to 1 week preceding catheterization (most within 72 hours). All AVA determinations were made without knowing the results of other studies.

Cardiac catheterization was performed through the femoral route using 7Fr balloon-tipped catheters in the right heart and 6Fr high-flow pigtail and Judkins or Amplatz coronary catheters in the left heart. Pressures were recorded through fluid-filled catheters with Statham P23 transducers. The zero reference level was set at midchest. The aortic valve was crossed in retrograde manner. After flushing, pressure was recorded continuously at a high chart speed (100 mm/s) in the left ventricle and during catheter pullback into the aorta. Cardiac output was determined directly thereafter as the average of 5 thermodilution measurements. The systolic ejection period and the mean pressure gradient were obtained using an x-y digitizer and superimposing ventricular and aortic pressure tracings of cycles with equal preceding QQ intervals. AVA was calculated using the Gorlin formula[1]; the data were averaged over ≥3 pairs of cardiac cycles. The calcification of the aortic valve was graded arbitrarily as mild, moderate or severe at fluoroscopy. Aortic cineangiography was performed and interpreted in the standard way to grade aortic regurgitation from nonexistent to severe (0 to 4/4). The coronary angiographic studies were filmed in multiple projections and interpreted visually. A diameter reduction >50% was considered a significant stenosis.

The echocardiographic and Doppler studies were performed with a Toshiba SSH 160A ultrasonograph.

TABLE I Summary of Invasive and Noninvasive Findings in 41 Patients with Valvular Aortic Stenosis

Measurement or Characteristic	Range	Mean ± SD
Right atrial pressure (mm Hg)	0–10	4 ± 2
Pulmonary artery systolic pressure (mm Hg)	13–100	25 ± 15
Pulmonary artery wedge pressure (mm Hg)	2–38	11 ± 7
Left ventricular peak systolic pressure (mm Hg)	132–299	204 ± 45
Left ventricular end-diastolic pressure (mm Hg)	5–44	18 ± 10
Mean systolic transvalvular gradient (mm Hg)	4–129	59 ± 32
Cardiac output (liters/min)	2.5–9.1	4.5 ± 1.1
Aortic valve area (cm^2)		
Catheterization (Gorlin formula) (n = 34)	0.30–1.90	0.80 ± 0.48
Doppler echocardiography (n = 39)	0.27–2.70	0.80 ± 0.50
Magnetic resonance imaging (n = 36)	0.23–3.00	0.80 ± 0.56
	No. of Pts.	%
Coronary artery disease		
3-vessel or left main disease	5	12
1- or 2-vessel disease	13	32
Aortic valve calcium		
Mild to moderate	26	63
Severe	11	27

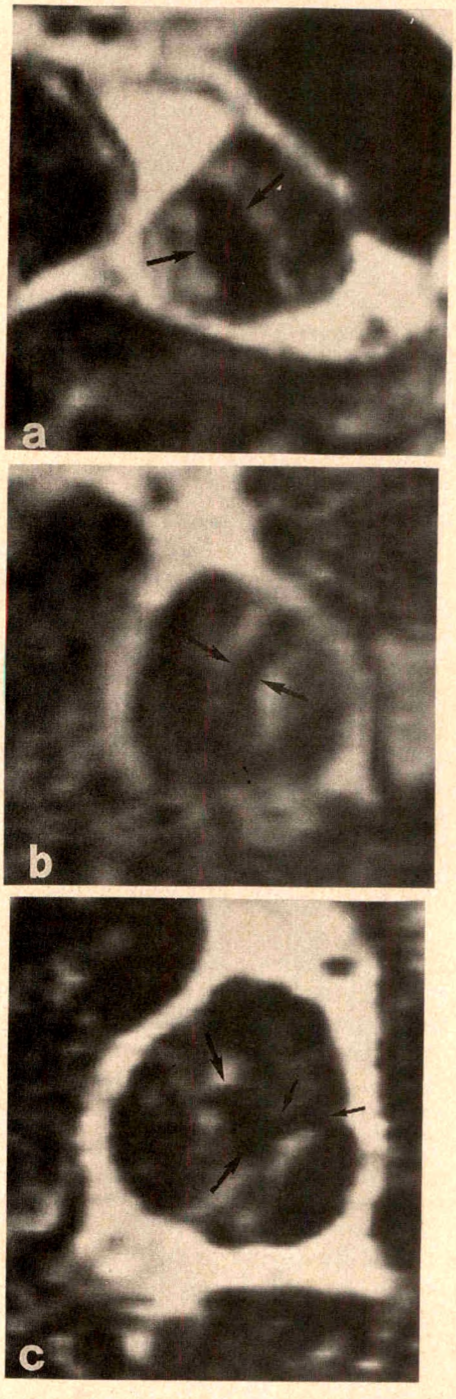

FIGURE 1. Examples of magnetic resonance images of systolic aortic valve orifices. *a and b*, bicuspid valves with orifice areas of 1.3 and 0.4 cm^2, respectively. *c*, tricuspid valve with an orifice area of 0.5 cm^2.

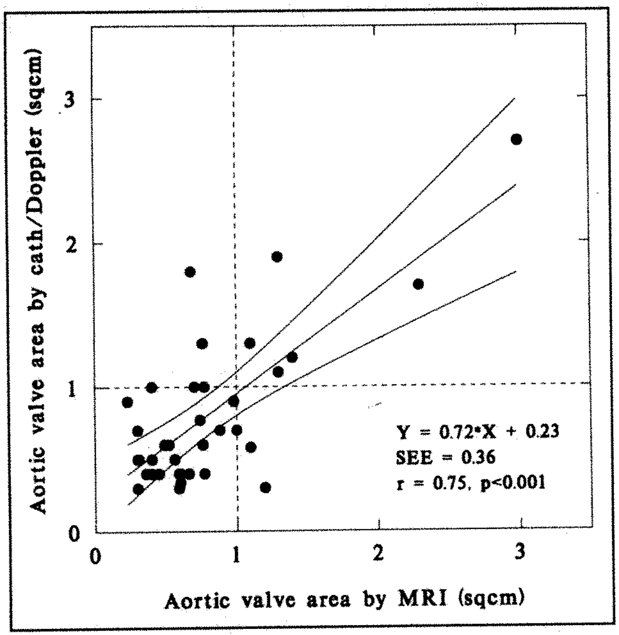

FIGURE 2. Aortic valve areas measured by magnetic resonance imaging (MRI) *(x axis)* plotted against the reference valve areas measured by catheterization (cath) or Doppler echocardiography *(y axis)*. The regression line and its 95% confidence intervals are also shown. SEE = standard error of estimate.

AVA was determined, using the continuity equation, from triplicate measurements of left ventricular outflow tract diameter and peak velocities in the outflow tract and in the stenosis jet.[2]

The MRI studies were performed using a 1.0 Tesla superconducting Siemens unit (Magnetom 42 SP) with body coil and cardiac gating. By means of a reconstruction diameter of 40 cm and a matrix of 128 × 256, the pixel size was calculated as 0.5 mm^2. *The resolution was a maximum of 1 pixel. The heart was first studied in the coronal plane using a spin-echo sequence (repetition time: RR interval – 150 ms; echo time, 15 ms; slice thickness, 8 mm) to determine the plane of the aortic valve. At this level, a coronal cine study (FISP-sequence, echo time 15 ms, repetition time 50 ms) was also performed to ensure accurate localization of the aortic annulus and valve orifice. To visualize the valve orifice in systole, an oblique transaxial spin-echo study using the same sequence was then performed by obtaining 7 contiguous 4 mm slices with 4 acquisitions, electrocardiographic gating and a delay time of 150 ms. Three lowest slices were timed to systole and the lowest one was carefully placed at the level of the aortic valve determined at end-systole in the earlier coronal spin-echo and cine MRI studies. The smallest of the 3 systolic AVA images was transferred to an image analysis system (Radgop/Wiz, Contextvision, Struers Vision AB). The valve orifice was outlined manually, and AVA was determined by multiplying the number of pixels by the pixel size.*

Of the 48 patients, 7 had more than minute $(>1/4)$ *aortic regurgitation at angiography despite our exclusion criteria; their data were deleted from all final analyses. The invasive, ultrasound and MRI findings in the remaining 41 patients are summarized in Table I. Five of them had not undergone the MRI study either because of restlessness, claustrophobia or technical failure, and 7 had incomplete data for invasive AVA determination. Figure 1 shows examples of MRI studies of aortic valve orifice in 3 patients. Figure 2 compares the AVA measurements by MRI* $(n = 36)$ *with the reference measurements obtained by catheterization* $(n = 31)$ *or Doppler ultrasound* $(n = 5)$*; the substitution of Doppler AVAs for missing invasive data was considered justified because of the close agreement between these techniques in the present study [Gorlin AVA* $(cm^2) = 1.00 \cdot$ *Doppler AVA + 0.02;* $n = 33$, $r = 0.93$, *SEE = 0.19]. Although the fit of the MRI data with the reference data was statistically highly significant, it was clinically less than satisfactory. If the cut point for severe AS was set at AVA* ≤ 1.0 cm^2 *(Figure 2), there were 2 false-positive and 2 false-negative MRI studies, whereas a cut point at* ≤ 0.8 cm^2 *had resulted in 5 false-negative and 6 false-positive MRI studies. We also compared the MRI and reference AVAs after excluding patients who had severe valve calcification at fluoroscopy* $(n = 11)$. *The fit of the data was essentially unchanged. In 5 randomly chosen patients, a blinded repeat analysis of the MRI study was performed. The AVAs of the 2 measurements were as follows (in* cm^2*): 0.6 to 1.0, 1.2 to 1.0, 0.8 to 1.0, 0.4 to 0.7, and 0.6 to 0.5. The root-mean-square difference was 0.26* cm^2.

We can think of several explanations for the less than ideal fit of the MRI data with the reference data in our study. First, we measured anatomic AVA with MRI, whereas both the Gorlin and the continuity equations quantify the functional AVA, i.e., the area occupied by effective flow.[4] Given a fixed anatomic AVA, functional AVA can change up to 20% depending on pressure and flow across the valve.[4] The true anatomic AVA had certainly been the best reference standard, but unfortunately it cannot be quantified unambiguously even at surgery because it varies considerably with changes of physiologic magnitude in the opening force.[5] For the same reason, anatomic AVA may not remain constant in vivo either.[5] These problems are particularly pertinent to our study because we compared nonsimultaneous measurements.

Calcium gives no signal in MRI and valve calcification may have distorted our MRI data. However, the fit of the data was independent of the degree of calcification, and in degenerative AS calcification frequently spares the free edges of the valve cusps.[6] A key question is whether the smallest orifice was included in the systolic slices of our MRI study in every patient. More than 1 study with differing transaxial sections of the aortic root should probably have been performed to ensure visualization of the critical systolic orifice. Image artifacts due to motion or MRI technology were also relatively common and caused difficulties in the ascertainment of the boundaries of the valve orifice in some patients. In retrospect, such studies should probably have been repeated to improve their quality. These factors also explain the less than ideal reproducibility of the AVA measurements by MRI.

In summary, we have shown that it is possible to directly visualize and quantify the orifice of the stenotic aortic valve using MRI. Our data indicate, however, that a number of details of the technique must be addressed and improved until it can be recommended for clinical use. In the near future, the possibility to measure flow velocities across the aortic valve will certainly also add to the utility of MRI in the study of patients with AS.

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Aortic or Mitral Valve Replacement in Systemic Lupus Erythematosus

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Although the true incidence of symptomatic valvulopathies in systemic lupus erythematosus (SLE) is unknown, cardiac involvement represents the third leading cause of death, surpassed only by infection and renal failure.[1] Surgical approach is appropriate palliation for symptomatic valvular disease in patients with SLE. Because of associated co-morbid conditions (i.e., multiorgan involvement from widespread microvasculitis), these patients are at greater risk for postoperative morbidity than are those undergoing similar operations. This report presents our experience in 7 patients with SLE who underwent cardiac valve replacement.

We retrospectively reviewed the hospital medical records and follow-up clinical charts of 7 patients with SLE with hemodynamically significant valve lesions who were treated by valve replacement at the Brigham and Women's Hospital between April 1983 and May 1991. During this period, there were 50 patients of a total of 1,200 diagnosed with SLE who were admitted with some degree of cardiac valve pathology. Patients who were not operated on were excluded. The 7 patients (all women, aged 25 to 66 years, mean 47) were diagnosed by the Departments of Rheumatology, Immunology and Cardiology, and fulfilled the criteria for SLE.[2] The extent of cardiac involvement was measured by 2-dimensional echocardiography and cardiac catheterization with coronary angiography in all patients. Excised valve tissues were available for pathology examination in all cases. Standard operative techniques were used for valve and homograft replacements on cardiopulmonary bypass.

The baseline profile data of the patients studied and the hemodynamic findings are summarized in Table I. All patients were symptomatic and had congestive heart failure whether progressive or sudden (functional class III and IV).

Four patients had anemia, 2 had systemic hypertension, 3 had chronic stable renal failure, and 1 had angina. Serum immunology revealed increased antibody titers in accordance with SLE; all patients had positive antinuclear antibody titers at the time of admission and were treated with steroids in varying dosages. Patient 1 had pleural effusion with low complement level typical of connective tissue pleural exudate. One patient had lupus hepatitis, and 1 had severe restrictive lung disease (35% predicted forced expiratory volume in 1 second/

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TABLE I Summary of Baseline Characteristics of Seven Women with Systemic Lupus Erythematosus

					Angiography		Hemodynamics					
Pt. No.	Age (yr)	Length of Time on Prednisone (yr)	Valve Lesion	Functional Class (NYHA)	MR (0–3+)	AR (0–3+)	CI (L/min/m^2)	EF (%)	LVEDP (mm Hg)	Anticardiolipin Antibodies (GPL units)	CH$_{50}$ (U/ml)	ANA (HEP$_2$) Anti-DNA Titer
1	66	4	MR	III	3	0	2.1	57	11	ND	260	+ at 1:640 + at 1:40
2	40	5	MR	IV	3	1	2.8	45	18	<22	239	+ at 1:2,560 1:10
3	65	5	AS	III	0	1	2.2	50	18	ND	240	+ at 1:160 0
4	34	10	AR*	III	0	3	4.7	51	38	ND	ND	ND
5	59	4	AR	III	2	3	2.5	66	22	<22	246	+ at 1:640 ND
6	44	7	AR	III	1	3	2.9	50	12	35	126	+ at 1:640 + at 1:320
7	25	11	AR & MR	IV	3	3	4.3	80	18	ND	ND	+ at 1:40 0

*Had associated coronary artery disease.
ANA = antinuclear antibodies; AR = aortic regurgitation; AS = aortic stenosis; CH$_{50}$ = total hemolytic complement; CI = cardiac index; EF = ejection fraction; HEP$_2$ = human epitheloid-2; LVEDP = left ventricular end-diastolic pressure; MR = mitral regurgitation; ND = not done on this admission; NYHA = New York Heart Association.

36% predicted forced vital capacity). An aortic homograft was used in patient 6, because of chronic anemia and to avoid anticoagulation.

No finding suggestive of Libman-Sacks endocarditis was seen at operation. Four aortic valves were trileaflets that had various degrees of calcium, diffuse fibrosis and thickening. Of 3 mitral valves replaced, 1 had thickened calcific leaflets and annulus, 1 had prolapsed anterior leaflet with contracture of the posterior medial commissure, and 1 had perforated anterior leaflet due to bacterial endocarditis.

At least 3 operatively excised valves had focal postinflammatory changes suggestive of chronic rheumatic heart disease, and the others variably had calcific or myxomatous degeneration. The 1 aortic stenosis found was caused by marked focal nodular calcification within the sinuses of valvula associated with diffuse thickening and fibrosis of all trileaflets consistent with senile calcific valvulopathy. No features suggestive of Libman-Sacks endocarditis were noted.

There was no 30-day or in-hospital mortality, and long-term follow-up was available in all 7 patients. The mean follow-up interval was 38 months (range 4 to 88), 2 late deaths from congestive heart failure occurred at 44 and 88 months, respectively, and 2 patients needed subsequent operations, including 1 orthotopic heart transplantation without event.

Aortic regurgitation is the most frequent clinical valve problem in SLE,[3] whereas mitral valve involvement prevails in autopsied patients. It remains to be clarified whether the presence of antiphospholipid antibodies directed against the heart is associated with a higher incidence of valvular lesions in patients with SLE. In the present series, this information was available in only 3 patients, and only 1 had an increased level of serum anticardiolipid titers. Libman-Sacks verrucous vegetations[4] are considered pathognomonic of valvular SLE. The valve pathology found in this series is not typical of valvular lesions generally ascribed to SLE; no patient had the typical Libman-Sacks lesions on the valves.

Homografts[5] are ideal for severe recalcitrant aortic valve endocarditis and need no anticoagulation. Furthermore, there is no incidence of thromboembolism and hemolysis. In this series, both mechanical and bioprosthetic valves were used. Valve selection was highly individualized in this patient cohort based on age and other medical complications. In patients with bleeding abnormalities, the superiority of porcine over mechanical valves is clear. However, we recommend that mechanical valve replacement be considered in patients at low risk with anticoagulation and at high risk for bioprosthetic valve calcification. When other factors are equal, we believe a mechanical prosthesis is preferable in this group of patients, especially if they have the lupus anticoagulant factor.

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Respiratory Influence on Doppler Estimation of Valvar Gradients in Congenital Pulmonic Stenosis

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We previously assessed right ventricular (RV) diastolic filling in normal neonates, infants, children and adolescents.[1–3] In those studies, we found significant respiratory variation in RV filling. We hypothesized that inspiration would increase the RV stroke volume and thereby increase the valvar pressure gradient in patients with congenital valvar pulmonic stenosis.

Sixteen infants and children with congenital valvar pulmonic stenosis (mean age 4.5 years; range 1 to 16) were evaluated. No patient had any additional cardiac defect (e.g., ventricular or atrial septal defects). None had congestive heart failure nor were any receiving cardiac medications at the time of the echocardiographic examination.

We performed complete 2-dimensional, Doppler and color Doppler echocardiographic examinations in each patient, using a Hewlett-Packard ultrasonoscope with a 5.0 or 3.5 MHz transducer and recorded the data using standard VHS format and thermal printing paper at a speed of 100 mm/s. Each patient underwent continuous-wave Doppler examination of the main pulmonary artery, either from a subcostal or lower parasternal approach, so that the interrogation beam was as close as possible to parallel with the pulmonary trunk. The electrocardiogram and respiration were simultaneously recorded with the Doppler examinations.[2,3]

We used a computer-interfaced digitizing tablet to obtain the following measurements for the pulmonary trunk in both end-expiration and end-inspiration: peak

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velocity and RR interval. From these measurements we computed the predicted peak valvar gradient and heart rate.

All values are reported as mean ± SD, using 3 measurements at both end-expiration and end-inspiration. Appropriate paired or unpaired t *tests were used for statistical analysis, and a p value <0.05 indicated a significant difference between groups.*

All patients in the study had congenital valvar pulmonic stenosis with no other structural cardiac defect. Some patients demonstrated mild tricuspid regurgitation by Doppler examination, but none had a dilated right ventricle or atrium, or clinically detectable tricuspid regurgitation.

The average peak velocity across the pulmonic valve was 2.42 m/s in expiration and 2.74 m/s in inspiration, which corresponded to peak pressure gradients of 25 and 32 torr, respectively (Figures 1 and 2). Using a paired t *test, this difference is significant at the p <0.00001 level. Peak velocity increased during inspiration in all 16 cases. The average change in peak velocity was an increase of 13%, whereas the average increase in predicted peak pressure gradient was 28%. The heart rate increased from an average of 94 beats/min during expiration to 100 beats/min during inspiration (Table I).*

We previously reported the normal patterns of RV diastolic filling in newborns[2] and in children aged 1.5 to 11 years.[1] In normal children age-matched to this study group, inspiration significantly increased RV filling.[2] Respiratory variation in RV filling was recently corroborated.[4] The RV diastolic filling pattern in patients with congenital valvar pulmonic stenosis is abnormal, demonstrating a greater dependence on atrial systole for RV filling.[5,6] We speculate that the increase in RV stroke volume in patients with pulmonic stenosis may actually be less than that seen in normal children. The normal subjects we reported previously[1,3] had an increase in RV filling of approximately 20 to 25% with inspiration, which would correspond to an increase in the transvalvar peak velocity of the same magnitude. This would correspond to an increase in the predicted valvar gradient of approximately 45 to 50%, based on the Bernoulli formula. The increased RV stiffness as a result of RV hypertrophy in patients with valvar pulmonic stenosis may limit enhancement of RV stroke volume with inspiration.

TABLE I Comparison of Respiratory Effects on Transvalvar Gradients in Congenital Valvar Pulmonic Stenosis

	Inspiration	Expiration	p Value
Peak velocity (m/s)	2.74 ± 0.18	2.42 ± 0.18	<0.00001
Predicted gradient (torr)	32 ± 4.2	25 ± 4.0	<0.00001
HR (beats/min)	100 ± 7	94 ± 6	<0.01

HR = heart rate.

Although no patient had additional cardiac defects, the presence of congestive heart failure or even subclinical RV failure could affect RV filling and the peak velocity of the Doppler shift.

With inspiration, there is enhanced systemic venous return to the right heart and an increased RV stroke volume. Furthermore, inspiration leads to decreased RV

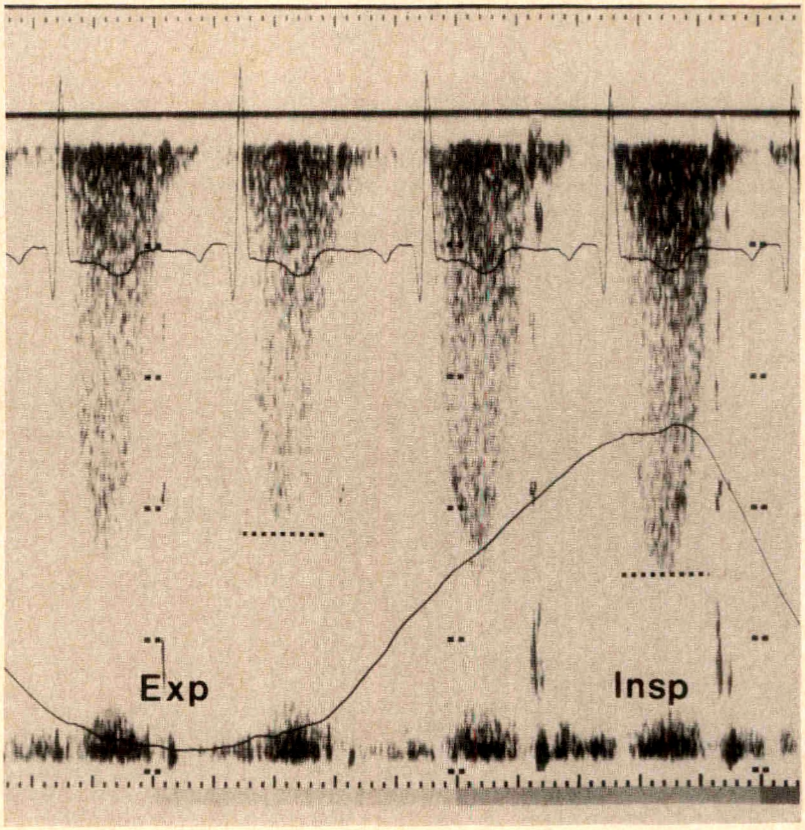

FIGURE 1. Doppler echocardiogram representing flow across pulmonic valve during inspiration (Insp) and expiration (Exp). Peak Doppler gradient increased from approximately 3.2 m/s during expiration to approximately 3.6 m/s during inspiration. Recording was obtained at 100 mm/s, and 1 m/s calibrations are shown, together with simultaneous electrocardiographic and respiratory recordings.

afterload and may also change the position of the interventricular septum, both of which could further enhance RV stroke volume.[7-9] In patients with valvar pulmonic stenosis, the increased stroke volume ejected through a fixed level of obstruction would lead to an increase in the peak Doppler shift across the pulmonic valve.

In clinical practice, the murmur of tricuspid insufficiency is enhanced with inspiration (Caravallo's sign). This study would predict a similar enhancement of the murmur of pulmonic stenosis with inspiration, because stroke volume and transvalvar gradient are both increased. It is possible the increased thoracic volume increases the distance from the sound source to the observer and thereby decreases the sound intensity at the upper left sternal border.

We conclude that there is significant respiratory variation in the Doppler shift across the pulmonic valve in patients with valvar pulmonic stenosis. Respiratory changes in the predicted transvalvar gradient are relatively modest and usually would not change clinical management.

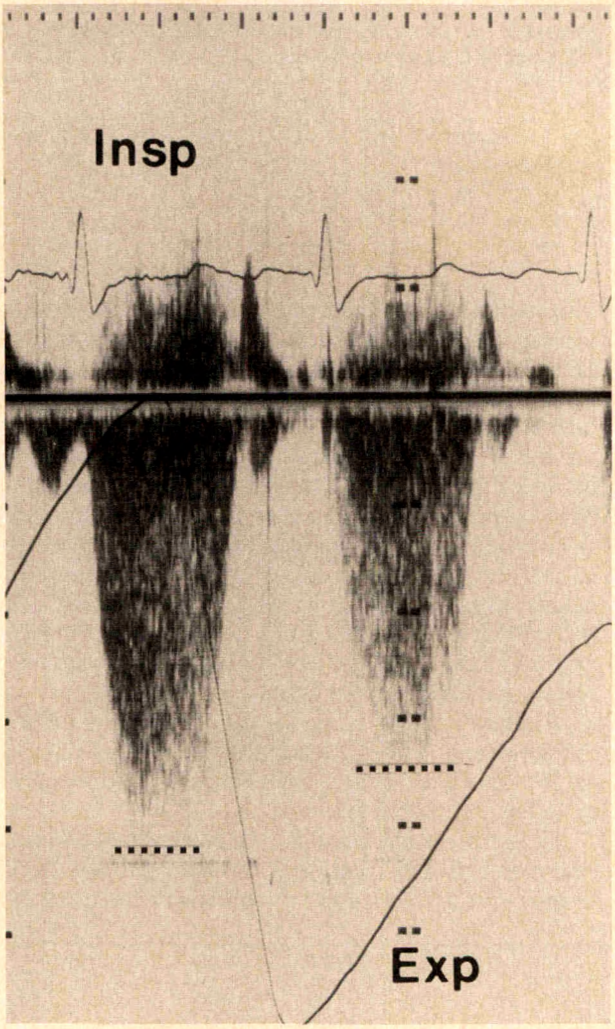

FIGURE 2. Doppler echocardiogram representing flow across pulmonic valve during inspiration (Insp) and expiration (Exp). Peak Doppler gradient increased from approximately 3.4 m/s during expiration to approximately 4.2 m/s during inspiration. Calibrations are shown at 1 m/s, and electrocardiogram and respiration are each recorded simultaneously with Doppler echocardiogram.

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Intravenous Enalaprilat and Oral Enalapril in Congestive Heart Failure Secondary to Ventricular Septal Defect in Infancy

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Successful management of congestive heart failure (CHF) in infants with a left-to-right shunt is difficult and medical therapy with digoxin and a diuretic drug is not always of sufficient benefit.[1-3] The magnitude of the shunt through a ventricular septal defect (VSD) is responsive to changes in systemic resistance, as shown in animals[4] and in infants after using hydralazine as an afterload-reducing agent.[5-7] The use of angiotensin-converting enzyme inhibitors for CHF of adults is well established,[8] and clinical studies in infants with left-to-right shunt and CHF suggest a beneficial effect.[9] Few hemodynamic data are available. We assessed the acute hemodynamic effects of enalaprilat given intravenously and the clinical benefits of oral enalapril in infants with a large VSD.

Eight infants, each with an isolated large VSD were studied (2 girls, 6 boys, age <10 months, median 2.9). Clinical and roentgenographic features of a large VSD and CHF were noted (respiratory rate >45 beats/min, liver >2 cm below the costal margin, weight <15 percentile). Some relevant clinical and hemodynamic data are listed in Table I. None received diuretic drugs. In 2 infants, treatment with digoxin was continued throughout the study, but discontinued 12 hours before catheterization.

After informed consent, infants were sedated (diazepam 0.5 mg/kg, ketamine hydrochloride 5 mg/kg) for cardiac catheterization. Hemodynamic data were measured and processed by a Quinton catheterization laboratory apparatus. Assessment included measurements of aortic, pulmonary capillary wedge, pulmonary artery and right atrial pressures. Oxygen saturations were measured in the aorta, the pulmonary artery, and the inferior and superior vena cava. Mixed venous oxygen content was estimated[10] and the pulmonary to systemic flow ratio was calculated in accordance with the Fick principle. Pulmonary output was measured by thermodilution with a technique based on analysis of the dilution curve before recirculation of the indicator by the left-to-right shunt.[11] Systemic output and the absolute shunt were derived from the pulmonary output and the pulmonary to systemic flow ratio. Superior vena caval blood samples were obtained to determine renin activity, aldosterone and atrial natriuretic peptide concentration. All data, controlled in 4 infants after 15 minutes steady state, did not change significantly from baseline determination. Before angiography, enalaprilat 0.02 mg/kg was administered intravenously over 1 minute. All data were obtained before and 15 minutes after administration of enalaprilat. Finally, left ventricular angiography confirmed a single large VSD (aortic root to VSD dimension ratio: 0.5 to 1.7, mean 0.75 ± 0.37).

One infant (patient 5) underwent surgery upon completion of the acute study because of increased pulmonary vascular resistance. Enalapril 0.16 mg/kg in 1 dose daily was administered to the 7 other infants for 7 days. Heart and respiration rates, weight and oral feeding were recorded. No infant received nasogastric tube feeding. Left ventricular dimensions were measured before enalapril and on the seventh day by echocardiography. Venous blood samples were obtained for measurement of aldosterone and renin concentration, and for hematologic, renal and liver function evaluation. The data were evaluated by the 2-tailed test for paired observations and considered significant at $p < 0.05$. Results are expressed as mean ± SD, and mean percentage of change with 95% confidence limits.

TABLE I Clinical and Hemodynamic Data Before Enalaprilat

Pt. No.	Age (mos)	Weight		RR	Qp/Qs Ratio	AO Pressure (mm Hg)	PA Pressure (mm Hg)
		Kg	Percentile				
1	1.7	4.1	16	64	3.0	87/47 (64)	51/16 (33)
2	4.2	5.4	9	60	3.7	66/49 (56)	53/23 (35)
3	1.0	3.6	15	65	3.2	82/43 (61)	72/35 (46)
4	1.6	3.5	5	67	5.7	79/45 (61)	48/32 (18)
5	10.0	5.9	1	59	1.7	86/50 (66)	87/53 (68)
6	3.5	4.2	2	56	4.1	105/53 (70)	53/15 (34)
7	2.4	3.9	4	48	1.6	99/45 (66)	41/14 (27)
8	6.5	6.5	5	45	2.4	119/57 (86)	85/32 (53)
Mean + SD	3.8 + 2.9	4.5 + 1	7 + 5	58 + 7	3.2 + 1.7	94/49 (67)	61/27 (41)

AO = aortic pressures, systolic/diastolic (mean); PA = pulmonary artery pressures, systolic/diastolic (mean); QP/QS = pulmonary-to-systemic flow ratio; RR = respiratory rate at rest.

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TABLE II Hemodynamic Measurements of Intravenous Enalaprilat in Eight Infants with a Large Left-to-Right Ventricular Shunt

Pt. No.	QS (L/min/m^2)			QP (L/min/m^2)			QP/QS			L-R Shunt (L/min/m^2)		
	C	E	%	C	E	%	C	E	%	C	E	%
1	2.93	2.0	−31	8.9	7.7	−14	3.0	3.8	25	5.9	5.6	−5
2	2.4	3.2	32	9.1	8.1	−11	3.7	2.5	−33	6.7	4.9	−27
3	2.6	2.5	−8	8.5	6.6	−22	3.2	2.7	−16	5.9	4.2	−29
4	4.4	3.4	−23	25.1	16.2	−36	5.7	4.8	−17	20.7	12.8	−38
5	3.1	3.2	3	5.3	4.7	−10	1.7	1.5	−12	2.2	1.6	−28
6	3.0	2.6	−13	12.7	9.5	−26	4.2	3.6	−14	9.7	6.8	−30
7	4.5	3.8	−16	7.2	6.8	−6	1.6	1.8	12	2.7	3.0	11
8	3.5	6.0	73	8.4	8.6	3	2.4	1.4	−41	4.9	2.6	−47
Mean ± SD	3.4 ± 0.7	3.5 ± 1.1	7	10.8 ± 6.6	8.6 ± 3.6	−15	3.2 ± 1.4	2.6 ± 1.2	−17	7.5 ± 6.3	5.0 ± 3.7	−27
CI		−25, +38			−3, −28			−2, −33			−10, −43	
p value		NS (0.7)			0.1			0.01			0.05	
No. of pts. (2–8)		7			7			7			7	

Pt No.	RA (mm Hg)			PA (mm Hg)			PCW (mm Hg)			AO (mm Hg)			RP (mm Hg/L/min/m^2)			RS (mm Hg/L/min/m^2)			RP/RS		
	C	E	%	C	E	%	C	E	%	C	E	%	C	E	%	C	E	%	C	E	%
1	2	2	0	33	32	−3	5	5	0	64	60	−6	3.16	3.52	11	21.1	28.7	36	0.15	0.12	−20
2	2	2	0	35	34	−3	8	12	50	56	54	−4	2.96	2.72	−8	22.1	16.1	−27	0.13	0.17	31
3	3	3	0	46	36	−22	6	6	0	61	54	−11	4.71	4.54	−4	22.3	20.4	−8	0.21	0.22	5
4	2	4	100	32	37	16	9	9	0	61	54	−11	0.92	1.73	88	13.3	15.1	14	0.07	0.11	57
5	3	3	0	68	60	−12	9	9	0	66	60	−9	11.17	10.76	−4	20.3	17.9	−12	0.55	0.60	9
6	3	5	67	34	27	−21	11	13	18	70	63	−10	1.81	1.48	−18	22.0	22.0	0	0.08	0.07	−12
7	4	1	−75	27	32	19	8	5	−38	66	61	−8	2.64	4.00	52	13.7	15.8	15	0.19	0.25	32
8	4	5	25	13	7	−46	13	7	−46	86	79	−8	4.77	3.96	−17	23.6	12.3	−48	0.20	0.32	60
Mean ± SD	3 ± 1	3 ± 1	17	42 ± 13	38 ± 9	−6	9 ± 2	9 ± 3	−2	67 ± 9	61 ± 9	−9	4.14 ± 2.90	4.17 ± 2.70	13	19.6 ± 3.7	17.1 ± 4.7	−9	0.20 ± 0.16	0.25 ± 0.17	25.5
CI		−35, +68			−22, +9			−32, +28			−6, −11			−25,+51			−30,+11			+2,−53	
p		NS (0.7)			NS (0.2)			NS (0.7)			0.0001			NS (0.9)			NS (0.2)			0.05	
No. of pts. (2–8)		7			7			7			7			7			7			7	

AO = aortic mean pressure; C = value before enalaprilat; CI = 95% confidence interval for mean change; E = data obtained 15 minutes after enalaprilat; L-R Shunt = left-to-right shunt; NS = not significant; PA = pulmonary artery mean pressure; PCW = pulmonary capillary wedge pressure; QP = pulmonary flow; QP/QS = pulmonary-to-systemic flow ratio; QS = systemic blood flow; RA = right atrial mean pressure; RP = pulmonary resistance; RP/RS = pulmonary-to-systemic resistance ratio; RS = systemic resistance.

After intravenous enalaprilat, 7 infants responded similarly; their results are discussed together (patients 2 to 8, Table II). Absolute left-to-right shunt decreased 27% (7.5 ± 6.3 to 5 ± 3.7 liters/min/m^2, $p < 0.05$). Systemic blood flow did not change, whereas pulmonary blood flow decreased 15.5% ($p < 0.1$), which resulted in a 17% mean decrease in the pulmonary to systemic flow ratio (3.2 ± 1.4 to 2.6 ± 1.2, $p < 0.01$). Mean decrease of aortic mean pressure was 9% (66 ± 9 to 61 ± 9 mm Hg, $p < 0.0001$). Pulmonary resistance remained unaffected, whereas systemic resistance was reduced causing a 25% increase in the pulmonary to systemic resistance ratio ($p < 0.05$). Heart rate, hemoglobin concentration, and right atrial, mean pulmonary artery and pulmonary capillary wedge pressures remained unchanged. Hormonal dosage showed a marked increased plasma renin activity (11 ± 12 to 17 ± 13 ng/ml/hour, $p < 0.05$), a decrease in aldosterone (2 ± 0.8 to 1.4 ± 0.9, $p < 0.1$) and atrial natriuretic peptide level (506 ± 386 to 285 ± 177 pg/ml, $p < 0.1$). The atrial natriuretic peptide level correlated with the pulmonary to systemic flow ratio ($r = 0.67$, $p < 0.005$).

In 1 infant (patient 1, Table II), a paradoxical response was obtained after enalaprilat administration: systemic blood flow decreased from 2.9 to 2 liters/min/m^2, pulmonary to systemic flow ratio increased from 3 to 3.8 and systemic resistance increased from 21 to 29 U.

After a 1-week trial with oral enalapril, the positive responders to intravenous enalaprilat (patients 2 to 4 and 6 to 8) had increased weight gain (82 ± 59 to 166 ± 94 g/week) and bottle feeding (milk, 139 ± 16 to 158 ± 13 ml/kg/day; $p < 0.05$). Patient 1, the negative responder to intravenous enalaprilat, experienced a deterioration in feeding pattern (milk, 110 to 80 ml/kg/day) and in weight gain (+125 to −80 g/week). The increase in feeding and in weight gain during oral treatment correlated strongly with the reduction in pulmonary to systemic flow ratio observed after intravenous enalaprilat ($r = 0.87$, $p < 0.01$ and $r = 0.74$, $p < 0.05$). M-mode echocardiography showed an increased shortening fraction (38 ± 3 to 42 ± 3%, $p < 0.05$). Aldosterone plasma level decreased 44% (95% confidence interval 26 to 58%) during oral therapy (2.6 ± 1 to 1.5 ± 0.4 nmol/liter, $p < 0.01$). Changes in heart and respiratory rates were not significant. The enalapril trial was well tolerated.

In infants with large VSD, the decrease in pulmonary resistance after birth results in a significant left-to-right shunt. Compensatory mechanisms allowing the preservation of an adequate systemic blood flow include renal activation of the renin-angiotensin system with secondary retention of salt and water.[12,13] Angiotensin and increased sympathic activity are involved in the increase in systemic resistance, with a secondary increase in left-to-right shunt. Both salt and water retention and left-to-right shunt cause volume overload of the left ventricle and CHF. Medical management must promote growth pending a possible spontaneous closure of the VSD[14] or surgical correction to avoid the hazards of pulmonary artery banding[15] and of surgical closure at an early age.[16] Medical therapy for CHF in infants remains a challenge. Digoxin and diuretics used for many years do not improve hemodynamics substantially in all infants.[1-3] Increasing hemoglobin concentration has a positive effect on left-to-right shunts,[17] but transfusion for this purpose has to be balanced with the risk of transmitted viral diseases. Alternative approaches using vasodilators have shown some positive results.[5,6] Converting enzyme inhibitor therapy is an attractive alternative. It diminishes renin-aldosterone hyperactivity and prevents fluid retention. A decrease in systemic resistance would reduce the left-to-right shunt.

The present study has documented favorable hemodynamic changes after enalaprilat; the pulmonary to systemic flow ratio decreased by 17% and the absolute left-to-right shunt by 27% as a result of the increase in pulmonary to systemic resistance ratio. These results are corroborated by a concomittant 33% decrease in atrial natriuretic peptide, a natural antagonist of the renin-angiotensin system[18,19] where concentration is correlated with pulmonary to systemic flow ratio and heart failure.[20,21] Aldosterone level also decreased after enalaprilat and after oral treatment.

During the oral enalapril trial, an increased gain in weight and bottle feeding were documented and correlated strongly with the hemodynamic response after intravenous enalaprilat. Although these results are not spectacular, they were obtained with low doses of enalapril.[22]

Patient 1 showed an unexpected paradoxical response, with a decrease in systemic cardiac output and an increase in systemic resistance after administration of intravenous enalaprilat. Atrial natriuretic peptide level increased also. This response was followed by weight loss and poor feeding during the oral trial with enalapril. One might speculate that a possible, more pronounced direct local action of enalapril on tissue-converting enzyme,[23] with consecutive sympathicolytic action at the heart level[24] and potentiated bradykinin activity,[25] resulted in impaired systolic function with low cardiac output, whereas an increase in sympathetic activity resulted in increased vascular resistance.

In conclusion, this study suggests a beneficial effect of angiotensin-converting enzyme inhibitors in the management of infants with a left-to-right ventricular shunt and CHF. Careful monitoring of the clinical response is needed before initiating long-term therapy.

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Diagnostic Value of Transesophageal Versus Transthoracic Echocardiography in Discrete Subaortic Stenosis

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Accurate diagnosis of discrete subaortic stenosis (DSS) is essential because it has unique prognostic and therapeutic implications. Clinical diagnosis is difficult and even angiography has been reported to diagnose only 59% of cases.[1] Conventional echocardiography including M-mode and 2-dimensional sector scanning frequently enable a definitive diagnosis to be made and almost always raise the possibility of DSS. Nevertheless, suboptimal patient imaging and limited instrument resolution, especially where the subaortic membrane is located in close proximity to the aortic valve, limit the sensitivity and specificity of transthoracic imaging (TTE). In this report we evaluate the utility of transesophageal echocardiography (TEE) in patients with DSS.

Between 1989 and 1992, 8 patients were seen in whom TTE either positively identified or raised the possibility of DSS. There were 2 male and 6 female patients (mean age 27 ± 14 years, range 14 to 56). A clinical diagnosis was not made in any of the patients. Two patients were assessed as having hypertrophic cardiomyopathy and the remainder as having valvar aortic stenosis. TTE studies were all performed by a single operator and in the left lateral decubitus position using a combination of 2.5, 3.5 or 5 MHz transducers attached to a commercially available imaging system (Hewlett-Packard Sonos 1000). TTE evaluation included detailed assessment of left ventricular outflow tract and aortic valve anatomy, Doppler measurement of outflow tract gradients, M-mode interrogation of the aortic valve, and quantification of aortic regurgitation by color flow mapping.[2] In the first 4 patients TEE was performed using a 5 MHz single plane probe and in the last 4 patients it was performed with a 5 MHz biplane probe (Ultramark ATL). All images were recorded on videotape and reviewed in a random and blinded manner by an experienced observer. Results are summarized in Table I.

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TABLE I Clinical and Echocardiographic Data

Pt. No.	Age (yr) & Sex	PCAV	TTE	AR (0–4)	AVG	TEE-SP	TEE-BP
1	33F	+	+	+2	52/99	+	
2	16F	–	–	+1	46/102	+	
3	13F	+	–	+1	42/50	–	+
4	33M	+	+	+1	11/17	–	+
5	15M	+	+	+2	35/55	+	+
6	56F	+	–	+2	29/65	+	
7	16F	+	–	+2	22/49	+	
8	31F	+	–	+1	89/51	–	+

AR = aortic regurgitation; AVG = mean and peak instantaneous left ventricular outflow tract gradient; PCAV = premature closure of the aortic valve; TEE-BP = membrane on biplane transesophageal echocardiography; TEE-SP = membrane on single plane transesophageal echocardiography; TTE = membrane on transthoracic echocardiography; + = membrane visualized; – = membrane not visualized.

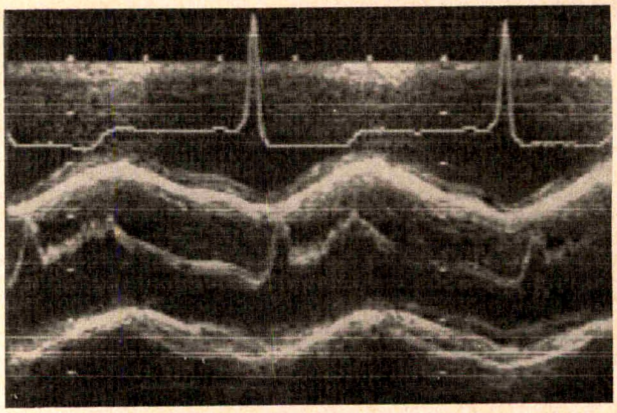

FIGURE 1. M-mode study of the aortic valve showing typical premature closure with systolic flutter of the aortic leaflets.

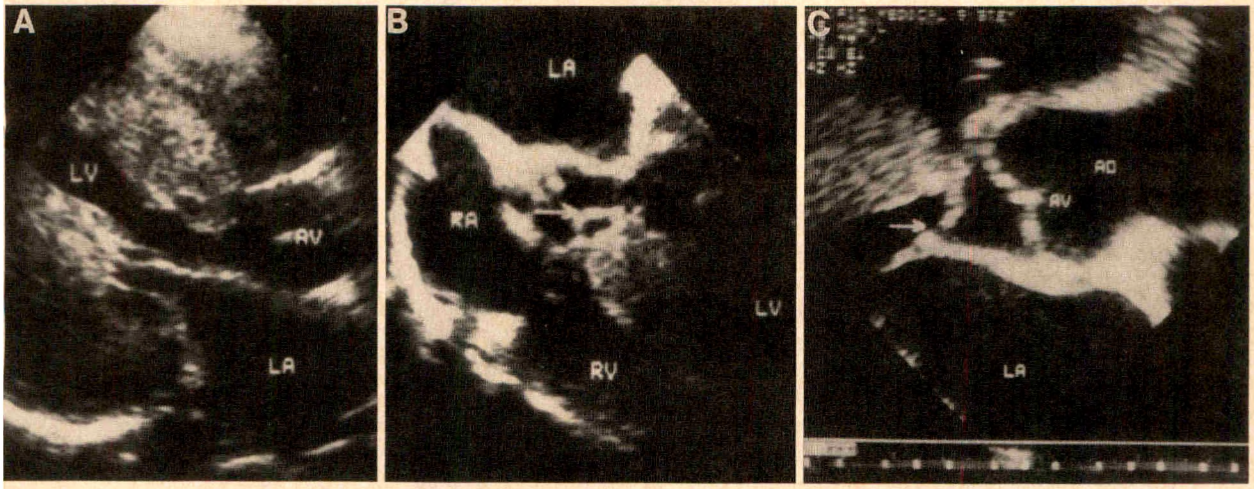

FIGURE 2. Parasternal long-axis view on transthoracic echocardiography (TTE) *(A)*, horizontal plane transesophageal echocardiography (TEE) *(B)* and longitudinal plane TEE *(C)* in the same patient showing failure to demonstrate membrane on TTE, suboptimal demonstration on horizontal plane imaging *(arrow)* and clear visualization on longitudinal plane *(arrow)*. AO = aorta; AV = aortic valve; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Premature closure of the aortic valve with systolic flutter (Figure 1) was seen in 7 of 8 patients. Clear visualization of the membrane on TTE, however, was only possible in 3 of 8 patients. Sensitivity of TTE could not be improved even after retrospective reevaluation (Figure 2A). Good quality Doppler outflow tract gradients were obtained in all patients. Demonstration of the subaortic membrane on TEE was possible in 5 of 8 horizontal and in 4 of 4 longitudinal plane examinations. Longitudinal plane TEE confirmed DSS in all 3 patients with a false-negative horizontal plane study.

Images obtained from the transverse plane always showed an oblique view of the membrane that was often difficult to distinguish from an aortic cusp (Figure 2B). Leftward flexion of the tip of the endoscope in the longitudinal plane into the long-axis view of the left ventricular outflow tract provided optimal demonstration of the membrane (Figure 2C). In all patients the membrane was seen as a discrete structure going down from the septal side of the left ventricular outflow tract and arising a variable distance below the aortic cusps. TEE allowed more precise definition of aortic valve morphology and aortic regurgitation on color flow mapping. However, assessment of outflow tract gradients was not possible in any of the patients because of the lack of continuous-wave Doppler and the inability to interrogate blood flow velocities in a parallel manner. Correlation between aortic regurgitation by TTE and TEE was good ($r = 0.9$, $p < 0.05$). Left ventricular angiography was performed in 3 patients (in 1 the membrane could be seen as a discrete radioluscent area below the aortic valve). Diagnosis of DSS was confirmed in all 3 patients who thus far have undergone surgery.

Reported sensitivities of TTE in visualizing the membrane in DSS vary from 14%[3] to 100%,[1] and probably reflect differences in methods of case selection. Factors limiting the sensitivity of TTE include suboptimal patient imaging, especially where the membrane is located in close proximity to the aortic valve. High resolution of TEE allows rapid and relatively noninvasive confirmation of the diagnosis.[4] Longitudinal scanning is particularly suitable because the membrane is imaged in a near perpendicular plane. Further advantages of TEE include enhanced definition of aortic valve structure and function that is crucial in defining the timing and type of surgery performed. Aortic regurgitation complicates 40% of cases of DSS and has a tendency to be progressive.[5] The presence of aortic regurgitation uniformly in our patients most probably is a reflection of their more advanced age and the greater sensitivity of TEE with color flow mapping compared with angiography. Although highly sensitive, premature closure of the aortic valve with systolic flutter on M-mode echocardiography lacks specificity, since it may occur in other conditions including ventricular septal defect and hypertrophic cardiomyopathy.[6] Erroneous diagnosis of hypertrophic cardiomyopathy in 2 of our patients emphasizes the similarity of the 2 conditions and the need for TEE because the management is very different. Based on this study we conclude that (1) TEE has a high degree of sensitivity for the diagnosis of DSS that supercedes that of TTE and even angiography; (2) longitudinal plane imaging is preferable to the horizontal plane; and (3) although TTE rarely allows a definitive diagnosis to be made it remains useful in raising that possibility.

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Comparison of Transesophageal and Transthoracic Echocardiography for Diagnosis of Right-Sided Cardiac Lesions

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Two-dimensional transthoracic echocardiography (TTE) is an established method for the evaluation of cardiac or paracardiac structural abnormalities such as tumors, vegetations and thrombi.[1-4] Cardiac structural resolution can be limited with TTE owing to anatomic interference. With transesophageal echocardiography (TEE), regions of the heart previously difficult to visualize are now readily studied. These regions include the vena cavae, right ventricular outflow tract, pulmonic valve and pulmonary trunk. The usefulness of TEE as compared with TTE in assessing right-sided cardiac pathology has not been clearly determined. We compared both techniques with the objectives of studying their diagnostic ability for the evaluation of right-sided cardiac lesions, and comparing data obtained with those from other confirmatory techniques.

In all, 47 hospitalized patients (27 women and 20 men, mean age 49 ± 20 years) referred to our laboratory with clinically suspected or incidentally found right-sided pathology underwent 56 TTE and TEE examinations. Indications included vegetation, thrombus, tumor and foreign body. Eight patients were imaged more than once. Additional confirmatory methods included blood cultures, pathologic specimens, computerized tomography, magnetic resonance imaging and nuclear scans.

All patients were studied with routine TTE and TEE using standard phased-array ultrasound imaging units (Acuson 128, Acuson Inc., Mountain View, California, or Hewlett-Packard SONOS 500, Hewlett-Packard Inc., Andover, Massachusetts). Both echocardiographic examinations were performed within 48 hours, after written consent and fasting for ≥6 hours. Cetacaine spray and midazolam hydrochloride were used for oropharyngeal anesthesia and sedation, respectively.

TEE identified nonartifactual abnormalities in 37 of 56 cases (67%) (Table I). TEE was consistent with the findings in all cases with confirmatory data available for comparison (n = 18; 49%) (6 vegetations, 6 thrombi, 5 tumors and 1 foreign body); TTE was consistent in 9 of 18 cases (50%) (4 vegetations, 3 thrombi, 2 tumors). Correlation of TTE with TEE data occurred in 3 of 19 cases (16%) with no confirmation. Among all cases, TTE correlated with TEE findings in 12 of 37 (32%). Echocardiographic diagnoses were not clinically suspected (incidental) in 9 patients (24%). Among all cases with nonartifactual abnormalities, TEE findings impacted on the management of 32 (86%), leading to alterations in anticoagulation (n = 15), antibiotic therapy (n = 8), surgery (n = 6) and tumor search (n = 3).

Nineteen TTE studies (33%) demonstrated abnormalities that were considered to be artifactual by TEE (small or narrowed superior vena cava, prominent right atrial appendage trabeculations, thickened tricuspid valve, intravenous lines, remnants of the superior vena caval valve, right atrial and ventricular wall indentation caused by localized pericardial effusions and prominent moderator bands). Figure 1 depicts the TEE of a suspected right atrial mass by TTE consistent with a small superior vena caval entrance into the right atrium.

Lesions identified in the right atrium and atrial appendage, and inferior and superior vena cava included thrombi, vegetations and tumors. Of 13 cases with right atrial thrombus, 5 were demonstrated by TTE and all by TEE. Figure 2 represents 1 such case.

Thrombi involving the vena cavae and entering the right atrium were delineated only by TEE in 3 cases (all related to in-dwelling central lines). In 2 patients with large vegetations within the right atrium attached to the

TABLE I Comparative Results of Transthoracic, Transesophageal and Other Confirmatory Data

Location	Cases	Lesion	TTE	TEE	Confirmation
Right atrial appendage	3	Thrombus	0/3	3/3	1/3
Right atrium					
Isolated right atrium	13	Thrombus	5/13	13/13	3/13
Superior and inferior vena cava	4	3 thrombi and 1 tumor	0/4	4/4	1/4
Tricuspid valve	1	Thrombus	0/1	1/1	0/1
Right ventricle, pulmonary trunk and pulmonic valve	2	Vegetation	2/2	2/2	1/2
Tricuspid valve	4	3 vegetations and 1 flail leaflet	3/4	4/4	3/4
Right ventricle	1	Foreign body	0/1	1/1	1/1
Pulmonary trunk	3	Thrombus	0/3	3/3	3/3
Pulmonic valve	1	Vegetation	0/1	1/1	1/1
Atrial septum	3	Tumor	2/3	3/3	2/3
Paracardiac	2	Tumor	0/2	2/2	2/2

TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

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tricuspid or pulmonic valve, TTE did not fully delineate the extent of the vegetations. Figure 3 illustrates a large enterococcal bacterial vegetation within the right atrium. Although TTE demonstrated the lesion contiguous to the tricuspid valve, TEE identified the attachment to the atrial septum and the absence of involvement of the tricuspid valve. A case of carcinoma invading the inferior vena cava and entering the right atrium was defined only by TEE. A dilated appendage containing thrombus in the presence of right ventricular volume overload was demonstrated only by TEE in 3 patients.

Lesions affecting the atrial septum, tricuspid and pulmonic valves, and pulmonary trunk were present in 11 cases; all were well-delineated by TEE, but only 5 by TTE.

A benign tumor and lymphomatous mass were described as right atrial and ventricular wall abnormalities, respectively, with TTE; TEE (with subsequent magnetic resonance imaging and computerized tomography) confirmed their extracardiac locations. A bullet fragment in the right ventricular wall was only demonstrated by TEE and was later found at surgery.

Ten of 20 patients with thrombi were known or found to have atrial shunting (1 atrial septal defect and 9 patent foramen ovale). In 8 additional cases, prosthetic material (valves or chronic in-dwelling lines) were present.

The major findings of this study are that: (1) TEE provides a higher diagnostic yield than does TTE for the identification of right-sided pathology, (2) TTE often leads to misdiagnosis due to anatomic artifacts, and (3) clinical management decisions concerning right-sided pathology can often be made after TEE.

The present report is the first systematic attempt to compare TEE with TTE in patients with right-sided cardiac pathology. In this series, TEE correlated in 18 of 37

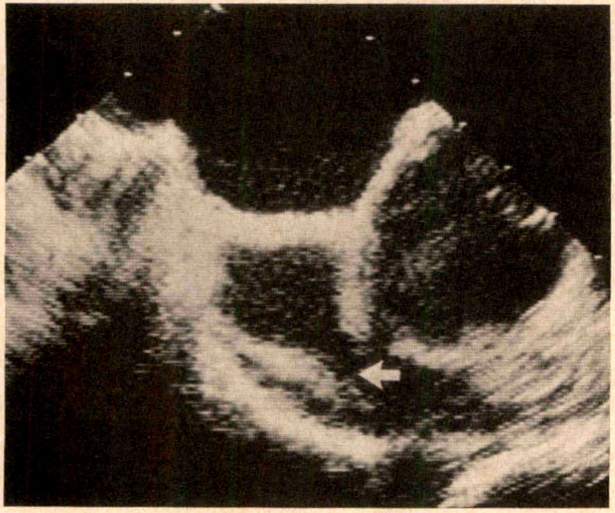

FIGURE 1. Frequently found "abnormality" within right atrium. Although transthoracic echocardiography often identifies this as pathologic structure, transesophageal echocardiography reveals small superior vena caval entrance into atrium *(arrow)*.

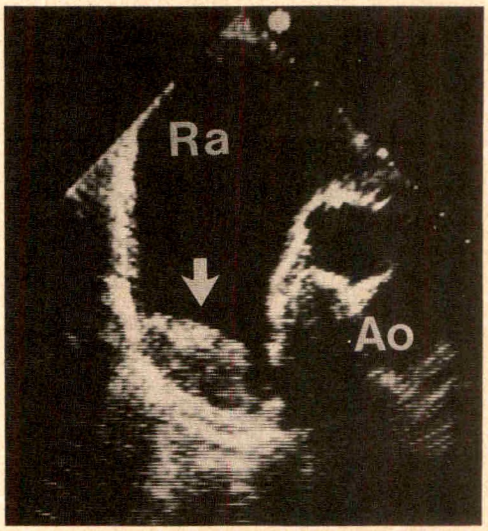

FIGURE 2. Large atrial thrombus *(arrow)* demonstrated by transesophageal echocardiography in patient with right ventricular volume overload. Transducer is located in upper to mid-esophagus. Ao = aorta; Ra = right atrium.

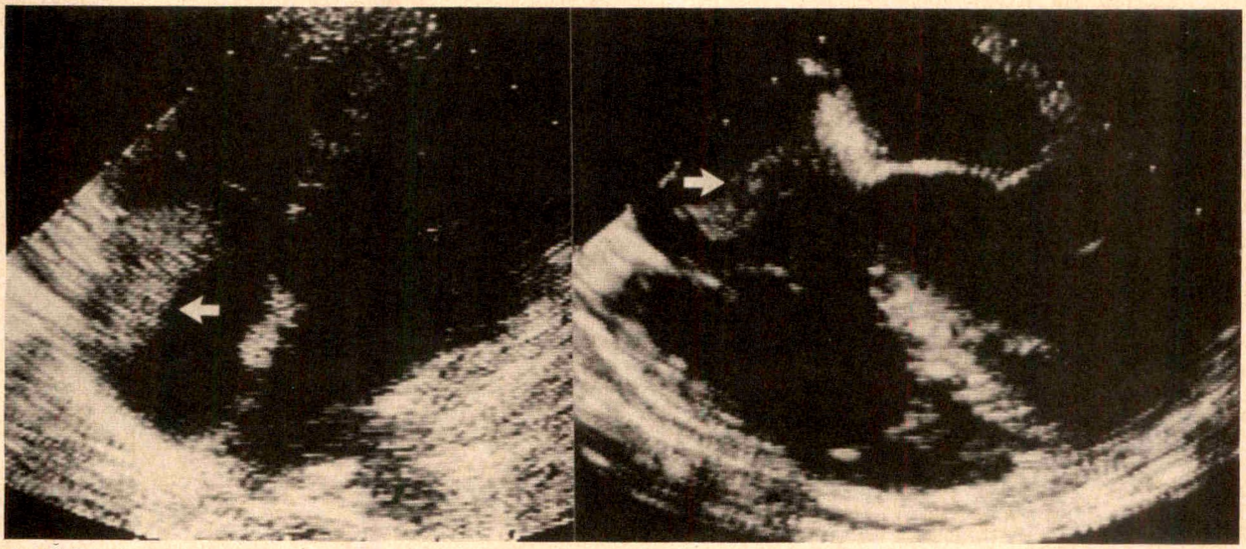

FIGURE 3. Large bacterial vegetation within right atrium. *Left,* apical transthoracic view demonstrates vegetation contiguous to tricuspid valve. *Right,* transesophageal echocardiogram identifies attachment point in atrial septum and absence of involvement of tricuspid valve (*arrows* identify vegetation).

cases with confirmatory techniques, with little agreement between TTE and confirmatory techniques. Our purpose was not to test the value of each echocardiographic modality in assessing anatomic complications; we attempted to compare both TEE and TTE for each right-sided location over a wide range of diagnoses.

Although TTE visualized right-sided anatomy, certain regions such as the right atrial appendage, superior vena cava and pulmonary trunk were not well seen. Furthermore, poor resolution and incorrect transducer angulation may have created the artifacts reported here. TEE may be a more reliable technique in assessing right heart lesions, because of the absence of thoracic interference, higher frequency ultrasound and improved visualization of posterior structures.

The tricuspid and pulmonic valves, and the pulmonary trunk are anterior to the heart and in the near field in respect to TTE transducers. However, in this series, TEE was more useful in 3 cases of pulmonary thromboembolic disease by defining mobility, location and relation of thrombus to lumen. A potential but undefined role for TEE in this disease has been suggested by other investigators.[5]

Mugge et al[6] recently reported the diagnostic potential of TEE in studying cardiac and paracardiac masses. In that study, although most patients had a correct diagnosis by TTE, identification of masses anterior to the heart and invading major vessels was improved by TEE. We reported 6 cases in which TTE did not help in the diagnosis. It incorrectly identified pericardial tumors, atrial septal hypertrophy and foreign body within the cardiac chambers. In these structures, computerized tomography and magnetic resonance imaging were consistent with the TEE findings.

In this study, TEE was useful in detecting associated, clinically relevant conditions such as atrial shunts, malfunctioning intravenous lines or prosthetic valves. We do not have confirmatory data in 50% of patients; however, among those who underwent additional diagnostic techniques, TEE findings correlated in all cases. Our cohort is skewed, because most patients were referred with suspected right-sided abnormalities. Consequently, sensitivity and specificity cannot be determined. The addition of biplane technology may increase the detection rate of abnormalities affecting the superior vena cava, right atrial appendage or pulmonary trunk.

In conclusion, given the unreliability of TTE in assessing right-sided cardiac lesions, if TTE does not demonstrate suspected pathology, TEE should be performed. In the absence of TEE, other confirmatory techniques such as magnetic resonance imaging and computerized tomography are recommended.

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Transesophageal Echocardiographic Detection of Abnormalities of the Tricuspid Valve in Adults Associated with Spontaneous Closure of Perimembranous Ventricular Septal Defect

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Perimembranous defects are the most frequent types of ventricular septal defect. Spontaneous closure of these defects occurs often in childhood. The mechanism of closure is controversial, but recent pathologic and clinical studies in children suggest that it occurs by reduplication and adhesion of the septal leaflet of the tricuspid valve to the margins of the defect.[1-2] Closure of the defect is frequently associated with the formation of a ventricular septal aneurysm, a term that describes an outpouching in the region of the membranous septum.[3] The adherent tricuspid valve protrudes into the right ventricle during ventricular systole, accounting for its aneurysmal appearance. Less frequently, prolapse of an aortic valve leaflet reduces the size of the defect and can result in aortic insufficiency.[1] Early pathologic studies demonstrated deformity of the tricuspid valve resulting from ventricular septal aneurysm formation.[4] Chordal shortening and fusion, and leaflet deformity have been demonstrated in necropsy examinations of patients with ventricular septal aneurysms. Functional abnormalities resulting from tricuspid valve involvement in the formation of the aneurysm were recently described in pediatric studies.[2] However, these abnormalities have not been described in adults, and the use of transesophageal echocardiography for the detection of ventricular septal aneurysms was not previously reported.

We report the findings in 4 adult patients with ventricular septal aneurysms who underwent transesophageal echocardiography (TEE) at our institution. Three patients had a childhood history of ventricular septal defect. The fourth patient was diagnosed as an adult by TEE, and the presence of a membranous ventricular septal defect was confirmed later at autopsy. Three patients had completely closed defects, and the fourth had a small shunt by Doppler color flow mapping. We relate the TEE findings in these patients to the mechanism of ventricular septal defect closure and subsequent alteration in tricuspid valve function.

The index case was a 27-year-old woman who presented with supraventricular tachycardia and had evidence of tricuspid insufficiency on physical examination. A surface echocardiogram showed moderate to severe tricuspid insufficiency and normal pulmonary artery pressure. A saline solution contrast study was negative for an intracardiac shunt. TEE was performed to determine the etiology of her tricuspid insufficiency and showed that the septal leaflet of the tricuspid valve was involved in the closure of a membranous ventricular septal defect. This resulted in deformity of the leaflet and a ventricular septal aneurysm (Figure 1). After review of the records of 520 consecutive outpatient TEE examinations from October 1988 to October 1991, 3 other patients with ventricular septal aneurysms were identified. The clinical and echocardiographic features of the 4 patients are summarized in Table I.

It is well-recognized that a substantial number of defects in the membranous ventricular septum spontaneously close or diminish in size during childhood. Early observations suggested that aneurysm formation was frequently associated with membranous ventricular septal defects in childhood.[5] Subsequently, aneurysm formation was thought to have a role in spontaneous diminution in size of membranous defects. Tandon and Edwards[6] described their autopsy findings of an aneurysm resulting from adhesion of the septal leaflet of the tricuspid valve to the margin of a membranous defect resulting in closure of the defect. The role of this mechanism in ventricular septal defect closure was confirmed by later pathologic and echocardio-

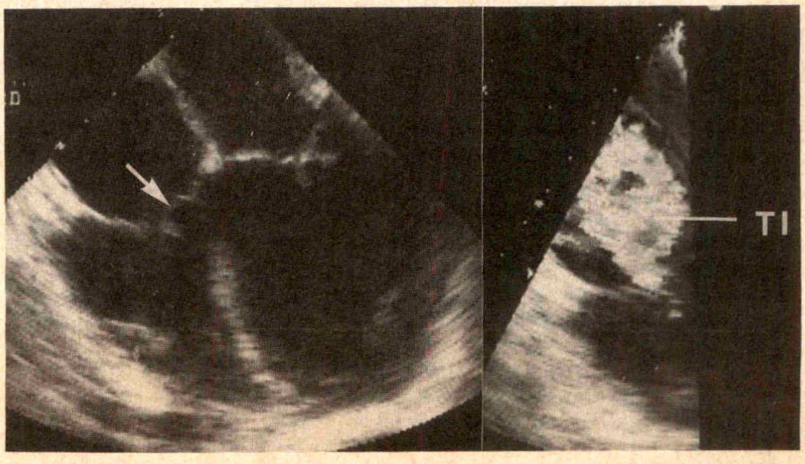

FIGURE 1. ***Left,*** **transesophageal echocardiogram showing 4-chamber view with deformed tricuspid valve *(arrow)* resulting from closure of membranous ventricular septal defect. *Right,* color flow Doppler from same patient showing moderate to severe tricuspid insufficiency (TI).**

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TABLE I Mechanism of Perimembranous Ventricular Septal Defect Closure

Age (yr) & Sex	VSA Detected by TTE	Mechanism of VSD Closure: Reduplication and/or Adhesion TV	Aortic Leaflet Prolapse	Tricuspid Insufficiency
27F	0	+	0	3–4+
31M*	0	+	0	2+
20F	0	+	0	1+
28M	+	+	0	0

*Patient died 1 year after echocardiogram from unrelated causes. Autopsy examination confirmed presence of 1.5 cm membranous ventricular septal defect that was completely closed by apposition of septal leaflet of tricuspid valve to defect.

TTE = transthoracic echocardiography; TV = tricuspid valve; VSA = ventricular septal aneurysm; VSD = ventricular septal defect.

graphic studies. In a necropsy series by Anderson et al,[1] 26 of 69 membranous ventricular septal defects (38%) had evidence of at least partial closure. The tricuspid valve was responsible for closure by either reduplication of tissue or adhesion of the septal leaflet to the defect in 22 of 26 cases (85%). Prolapse of an aortic valve leaflet was the mechanism for reduction of the defect size in 3 of 26 cases (12%). The mechanism by which the tricuspid valve closes the defect is postulated to involve endothelial roughening of the tricuspid valve and the margins of the defect by the left to right shunt. Eventual adhesion of the surfaces occurs and closes the defect.[7]

Despite the recognition that the tricuspid valve is involved in the closure of membranous ventricular septal defects, few studies have evaluated the resulting functional abnormalities. Eshaghpour et al[8] used phonocardiography to demonstrate the association of tricuspid insufficiency with ventricular septal aneurysm formation and speculated that insufficiency may result from a mechanical disturbance caused by involvement of the tricuspid valve in aneurysm formation. Hornberger et al[9] recently observed 6 patients with significant diminution of ventricular septal defect size on serial surface echocardiographic examinations. They found a progressive increase in tricuspid insufficiency as the defect became smaller. Finally, Magherini et al[2] reported that significant tricuspid insufficiency was detected by pulse wave Doppler examination in 78% of patients with "restrictive" tissue in the area of a membranous ventricular septal defect. They concluded that tricuspid valve dysfunction was the result of the septal leaflet being involved in the closure of the membranous defect. All these studies were performed in children. There have been no studies in adults.

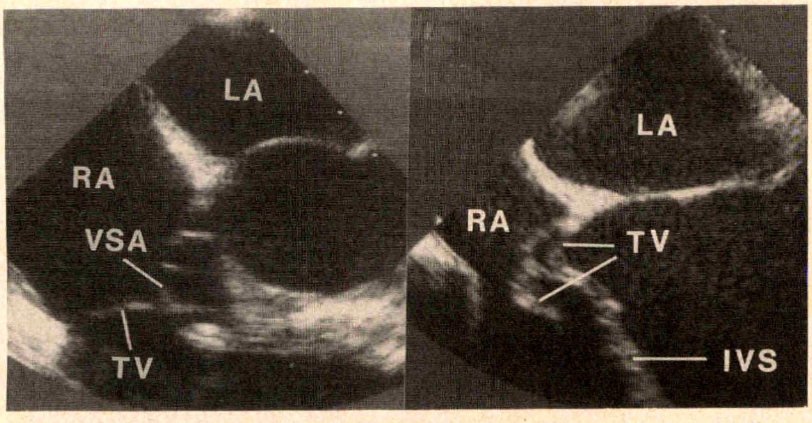

FIGURE 2. ***Left,*** **transesophageal echocardiogram showing ventricular septal aneurysm (VSA) that resulted in closure of membranous ventricular septal defect.** ***Right,*** **magnified view of tricuspid valve (TV) showing reduplication of valve tissue with adhesion to margins of membranous ventricular septal defect. Autopsy examination later confirmed these findings. IVS = interventricular septum; LA = left atrium; RA = right atrium.**

Echocardiography is the most sensitive method of identifying ventricular septal aneurysms.[10] Our findings suggest that TEE, with its superior image resolution, is an even more sensitive method than transthoracic echocardiography for their detection. Furthermore, TEE enabled better visualization of the anatomic structures that formed the ventricular septal aneurysms in these patients. In each patient, the tricuspid valve could be seen forming the aneurysm and closing the ventricular septal defect. In 3 patients, reduplication of the septal leaflet could clearly be seen (Figure 2). The resulting tricuspid valve deformity was associated with at least moderate tricuspid insufficiency in 2 of 4 patients. No patient had prolapse of an aortic leaflet or aortic insufficiency detected. These findings are similar to results reported in the pediatric literature. In adults, tricuspid valve participation in membranous ventricular septal defect closure may be a more frequent cause of isolated tricuspid insufficiency than has been appreciated.

We conclude that TEE is a sensitive method for the detection of ventricular septal aneurysms. Furthermore, tricuspid insufficiency can result from closure of membranous ventricular septal defects. TEE to detect a ventricular septal aneurysm should be considered in patients with unexplained tricuspid insufficiency, particularly if there is history of a childhood murmur.

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A Symposium: Heart Failure Management in the 1990s: The Role of Lisinopril

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The American Journal of Cardiology

Introduction

Lars Rydén, MD

One of the reasons why I thought it was appropriate to accept the invitation to be guest editor of this symposium is shown in Figure 1. This illustrates the findings of an epidemiologic study in the Gothenburg area of Sweden that investigated the number of congestive heart failure (CHF) patients over time from 1970 to 1985. Although myocardial infarction rates declined for men and women, there was a constant increase in the numbers of patients diagnosed with CHF, despite improvements in treatment of hypertension and myocardial infarction.[1] This may be due to patients living longer and getting older and, thus, developing CHF. It is an increasing problem that is very important, since it is very costly for society and a large burden for the patient.

The pattern of the etiology of heart failure has also changed. Figure 2 shows that angina pectoris and myocardial infarction are the two major causes of CHF at present. Hypertension was previously a much more important factor.[1]

It was known relatively early that CHF in both men and women produced very poor life expectancy (Figure 3) in comparison to the total population.[2] This poor prognosis remains today, although we have made some improvements in therapy. During the last few years, there have been considerable efforts aimed at influencing mortality. Figure 4 shows the two alternative modes of cardiac death (sudden cardiac death and progressive heart failure), which are believed to be due to ventricular tachyarrhythmia and poor myocardial performance. Treatments employed in intervention against these mechanisms include antiarrhythmic drugs, inotropic agents, and other agents such as vasodilators and inhibitors of the renin–angiotensin system that may interact with both mechanisms. There have been some promising studies and one of the most widely quoted is the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I), which demonstrated a 36% reduction in mortality with the angiotensin-converting enzyme (ACE) inhibitor enalapril versus placebo in patients with advanced heart failure.[3] Other studies that demonstrated similar findings were the Veterans Administration Vasodilator–Heart Failure Trials (V-HeFT I and II). In V-HeFT I the combination of the vasodilators hydralazine and isosorbide dinitrate reduced mortality in comparison to placebo in patients with mild-to-moderate heart failure who were treated with digoxin and diuretics.[4] A second trial (V-HeFT II) demonstrated that reduction in mortality with enalapril was significantly greater than with hydralazine plus isosorbide dinitrate.[5] Finally, the Studies of Left Ventricular Dysfunction investigated hospitalizations for heart failure and mortality, and throughout a 48-month period there was a definite reduction in risk brought about by ACE inhibition.[6]

Thus, over the last few years, we have received important information that seems to tell us that we

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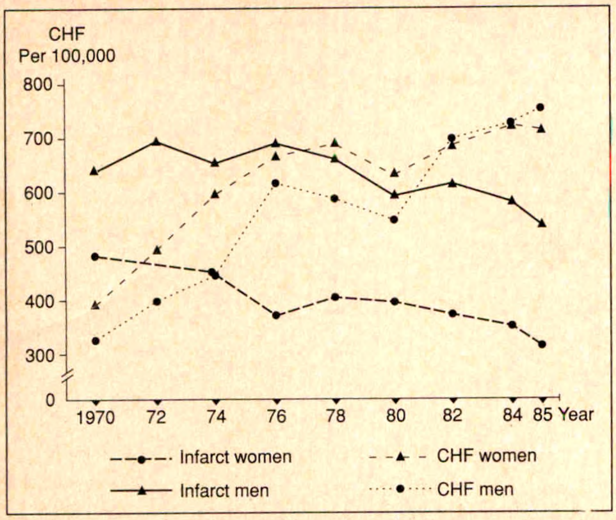

FIGURE 1. Incidence rates for congestive heart failure (CHF) and myocardial infarction in the Gothenburg area of Sweden 1970–1985. (Reprinted with permission from Eriksson.[1])

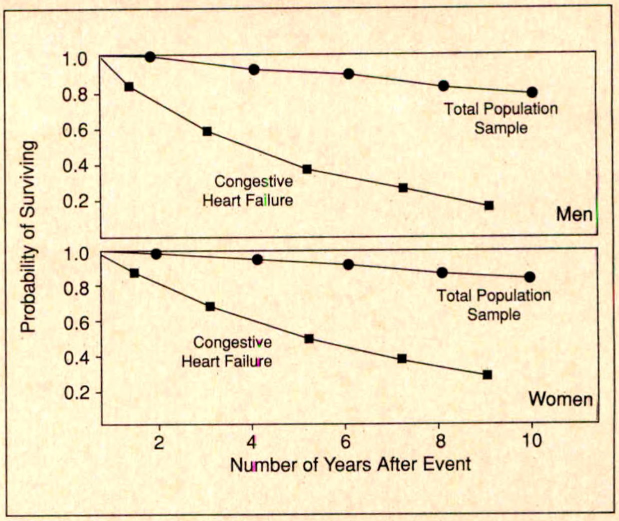

FIGURE 3. Comparisons of survival between men and women with congestive heart failure and the total population in the Framingham study. (Adapted from information appearing in the *N Engl J Med*.[2])

need to use ACE inhibitors if we hope to reduce mortality. We need to use them for mild and moderate heart failure and through to the final stages, as demonstrated in the CONSENSUS I study. We also now know that inotropic stimulation has a negative effect on mortality, and that antiarrhythmics seem to have no effect or actually negative effects. An important topic is thus to address why vasodilators and inhibitors of the renin–angiotensin system act in this way, and not inotropes or antiarrhythmics, and what could be the mechanism of action?

Within Europe, there are quite different patterns of usage of drug therapy for heart failure. For example, in Germany cardiac glycosides are widely used, whereas a higher percentage of patients are treated with diuretics in the United Kingdom. Overall, in Italy, France, Germany, and the United Kingdom, ACE inhibitors are not widely used in the treatment of patients with heart failure. For this reason, there seemed to be a need for clinicians to meet and discuss whether it is time to change treatment standards in heart failure and, if so, in which direction and how to make the change.

The first articles in this symposium will address the frontiers of research into heart failure from a clinician's point of view. Arrhythmias still provide a challenge in heart failure. However, the pathogenesis of ventricular tachyarrhythmias may be related to electrophysiologic and myocardial factors, electrolyte depletion, drugs, and neurohumoral factors. Therefore, it is important to obtain an overview of what is really known about arrhythmias in

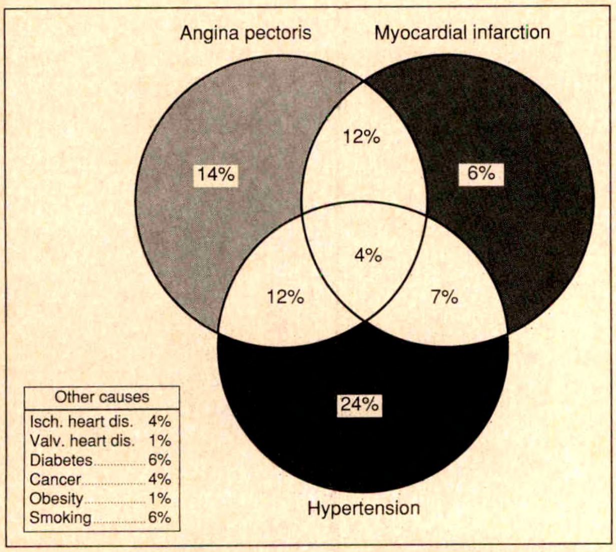

FIGURE 2. Diagrammatic representation of the principal causes of congestive heart failure (CHF) in 84 men with manifest CHF at the age of 67 years. (Reprinted with permission from Eriksson.[1])

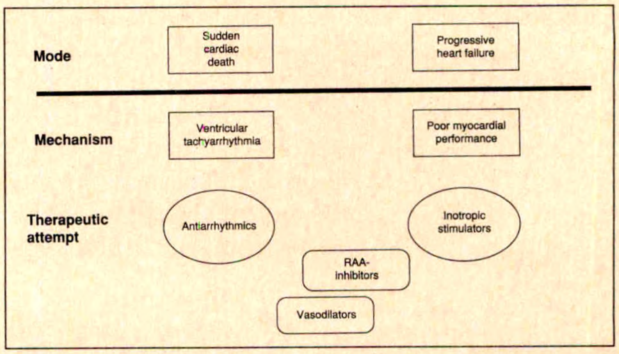

FIGURE 4. Causes of death and therapeutic modalities in congestive heart failure.

heart failure in order to determine whether it is possible to achieve a greater impact on sudden death, since about half of the patients die suddenly in heart failure. The extension of the role of ACE inhibitors in heart failure is covered by the articles that examine the effects on the peripheral circulation, left ventricular dysfunction in early heart failure, and use after myocardial infarction. The most recent efficacy and safety findings from clinical studies with the ACE inhibitor lisinopril and examinations of molecular issues such as structure–activity and dose–response relationships, drug–patient interactions and effects of ACE inhibitors on renal function are also presented in this symposium. In addition, Arnold Katz presents his opinions on the next 10 years of heart failure research and therapy.

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Autocrine and Paracrine Mechanisms in the Pathophysiology of Heart Failure

Victor J. Dzau, MD

At the cellular and molecular level the transition to heart failure is a complex process that involves structural adaptation, not only of the heart, but of peripheral vasculature and renal tissues as well. Recent studies have suggested that autocrine, paracrine, and circulating biologically active mediators activate events that result in the concerted failure of adaptive mechanisms and the ultimate depression of cardiac myocyte function. Greater understanding of these local mechanisms in the future may lead to drug therapies that can selectively block these mechanisms and prevent the progression from compensation to overt heart failure.

(Am J Cardiol 1992;70:4C–11C)

In recent years research on the natural history of heart failure has benefited from the application of cell and molecular biology techniques. Insights from previous physiologic studies on the development of pathologic hypertrophy have led to the view that hypertrophy is initially compensatory, permitting the heart to cope with increased loads secondary to pressure or volume increases. Molecular studies have shown that the mechanism of cardiac hypertrophy involves the remodeling of all cardiac tissue compartments (myocytes, matrix, and vasculature). This involves enlargement (hypertrophy) of cardiac myocytes, modulation of extracellular matrix, and possibly an increase in capillary density. The hypertrophy of cardiac myocytes in cardiac hypertrophy and failure is associated with a molecular expression profile similar to the fetal phenotype. Investigative efforts have largely focused, on the one hand, on the genetic regulation of myocyte contractile protein expression during cardiac hypertrophy and, on the other hand, on neuroendocrine activation in advanced heart failure. However, the transition to heart failure is a complex process that involves structural adaptation not only of the cardiac myocytes, but of extracellular matrix, peripheral vasculature, and the kidney as well. An understanding of the molecular mechanisms that activate these complex events is the key to any therapeutic strategy for heart failure prevention.

Neuroendocrine systems have been implicated in the pathophysiology of overt heart failure. However, they are not invariably activated in asymptomatic ventricular dysfunction. Recent studies have suggested that autocrine and paracrine mechanisms and circulating polypeptides may mediate the local events that result in the concerted failure of the adaptive mechanisms and the ultimate depression of cardiac myocyte function. It is also apparent that particular cellular and molecular circumstances in part determine the action of peptide and other mediators on their target cells.[1] Addressing the scientific basis for the transition to heart failure, therefore, requires research that

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takes an encompassing view of the cardiac milieu while attempting to elucidate the specific mechanisms involved. Molecular clues to the transition from compensated ventricular dysfunction to overt heart failure have recently come from evidence that the physiologic function of the myocardium is modulated through complex crosstalk among vascular, interstitial, and myocyte compartments of the heart. Thus, locally produced mediators can act in an autocrine manner or paracrine fashion to inform neighboring cells about local conditions and modify biochemical events that influence structure and function. More research is required to understand the mechanisms of the cell–cell interactions that may have important pathophysiologic roles in the initial adaptation and the subsequent transition to heart failure and to understand how such locally acting peptides mediate both structural and functional remodeling in the failing heart. Research is also needed to understand how circulating peptide hormones interact with the local mechanisms in the heart, blood vessel, and kidney to regulate ventricular function, vascular impedance, and fluid volume in the presence of a failing myocardium. For example, the vasoconstrictor effects of endothelin and the renin–angiotensin systems may be adaptively important in the early stages of heart failure because they contribute to the maintenance of perfusion pressure. However, the chronic effects of endothelin and renin–angiotensin system activation, including their actions as growth-promoting factors, may account for the progressive cardiac remodeling and functional deterioration to congestive heart failure.

This article will review what is known of the autocrine/paracrine mechanisms in the heart and present a hypothesis concerning their potential roles in the pathophysiology of heart failure, particularly in the transition from compensated ventricular dysfunction to overt heart failure.

THE CONCEPT OF A BALANCE OF FORCES

Rather than viewing heart failure in the traditional neuroendocrine way, the disease can be examined in terms of the local mechanisms that are activated within the myocardium and the microvasculature, which are believed to play an important role in making the transition from the clinically compensated state to overt heart failure. It is well recognized that a significant reduction in cardiac output and an increase in left ventricular end-diastolic pressure can activate peripheral compensatory mechanisms, which are mediated by neurogenic and endocrine systems. These include the renin–angiotensin system and the sympathetic nervous system, which, when activated, produce increases in systemic vascular resistance (afterload) and increases in preload through venoconstriction and sodium retention. Ordinarily, these are important compensatory mechanisms when cardiac output falls, i.e., they maintain blood pressure and also improve stroke volume. In the heart failure situation these increases in preload and afterload actually result in worsening of heart failure by increasing impedance to ejection as well as increasing filling pressure.

However, the neuroendocrine system is not always activated in compensated ventricular dysfunction.[2] After myocardial injury, there is an initial activation of the endocrine systems (atrial natriuretic peptide [ANP], renin–angiotensin system, and vasopressin) but usually these systems return toward normal as recovery occurs and cardiovascular compensation is achieved. During this compensated phase, it has frequently been demonstrated that the neuroendocrine systems are either slightly elevated or not at all. It is not until the transition into overt severe heart failure that the systemic endocrine systems become activated again. It is apparent that a long quiescent phase exists between initial injury, hemodynamic compensation, and overt heart failure. During this phase, many subclinical pathophysiologic processes occur, including cardiac and vascular remodeling, altered cardiac and vascular function, and renal sodium retention, despite an absence of neuroendocrine activation. What could be responsible for the transition to overt heart failure? I propose that local autocrine/paracrine systems play an important role, in terms of both adaptive and maladaptive mechanisms during this phase, and that pathologic activation of these systems eventually push the heart into overt heart failure.

Recent work has shown that, in addition to the neuroendocrine system, there are local systems that play important roles in the regulation of cardiac, vascular and renal functions. These are known as *autocrine* ("action on own cells") and *paracrine* ("action on adjacent tissues") systems. These include angiotensin, endothelin, peptide growth factors, endothelium-derived relaxing factor (EDRF), ANP, and prostacyclin, which are also generated locally in the myocardium either by cardiac myocytes, mesenchymal cells, or microvascular cells. Many of these factors are known to exert effects on vascular tone. Here, the balance between the constrictor and dilator systems is responsible for maintenance of myocardial mi-

TABLE I Vascular Tone and Remodeling of Congestive Heart Failure

Constrictor/Progrowth	Dilator/Antigrowth
Neuroendocrine	
Renin–angiotensin	ANP
Sympathetic–adrenal	
Vasopressin	
Local (autocrine and paracrine)	
Angiotensin	EDRF
Endothelin	PGI_2/PGE_2

ANP = atrial natriuretic peptide; EDRF = endothelin-derived relaxing factor; PGE_2 = prostaglandin E_2; PGI_2 = prostacyclin.

crovascular blood flow, and it is the imbalance of these two forces in favor of the vasoconstrictor hormones that may result in impaired perfusion and myocardial oxygen consumption and consequently worsen cardiac function.

Local compensatory mechanisms in the heart, kidney, and blood vessels may also play important roles in the pathophysiology of heart failure through their involvement in cardiac contractility (inotropic state) and ventricular remodeling. As in the control of the vasculature, a "balance of forces" between local and systemic positive inotropic factors and negative inotropic factors may also exist. The factors that influence vascular tone may also regulate cardiac contractility and structure (Table I). Positive inotropic factors include angiotensin (generated within the heart as well as in the circulation), catecholamines (in the circulation and released by sympathetic neurons), and endothelin (produced by blood vessels within the myocardium). These substances, if produced locally in excess of circulating levels, may have a direct compensatory inotropic effect on a poorly contracting heart. In contrast, the vasorelaxants, e.g., EDRF released by the endothelium of the microvasculature within the myocardium and the ANP expressed by the atrium as well as the ventricle during heart failure, can exert negative inotropic effects. Once again, the balance between these forces determines ultimately the state of contractility of the heart.

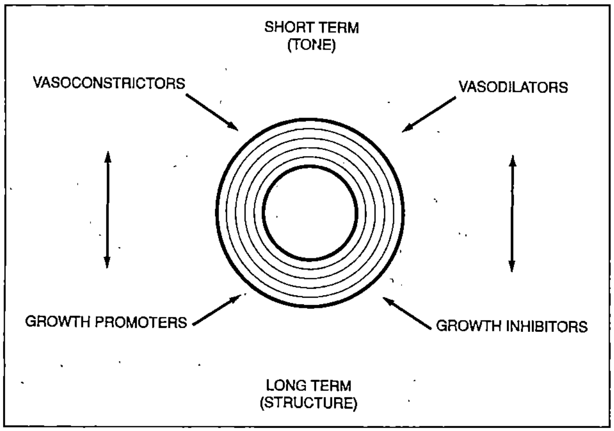

FIGURE 1. Schematic representation of the concept of balance of forces in the transition to overt heart failure.

Further to the issue of contractility is the process of cardiac remodeling. In order for the failing heart to maintain a normal wall stress and adequate stroke volume, it has to remodel. In the case of the myocardium, the myocytes, the microvasculature, the mesenchymal cells, and the interstitial matrix all participate in the restructuring of the ventricle. More recently, it has been shown that peptide growth factors expressed in the heart are involved with the molecular mechanism of cardiac remodeling. These include transforming growth factor-β, acidic and basic fibroblast growth factor, angiotensin II, and endothelin, which can promote cardiac myocyte growth, as well as ANP and EDRF (nonpeptides), which may inhibit cell growth. Here, once again, the same theme of a balance of opposing forces prevails, and it is this fine balance that modifies and decides whether the heart will be remodeled and eventually dilated.

In summary, under normal conditions at the local tissue (heart, vessel, and kidney) level, there is a balance between autocrine and paracrine constrictors and dilators (vascular system) in the regulation of vascular tone, between positive and negative inotropic factors (heart) in the control of contractility, and between endogenous growth promoters and inhibitors in the modulation of cardiovascular structure (Figure 1). Interestingly, these systems appear to be quite economic, since most of these factors have multiple biologic functions.

Indeed, many of the vasoconstrictors are also positive inotropes and growth promoters, e.g., angiotensin and endothelin, and many of the vasodilators may also act as negative inotropes and growth inhibitors, e.g., EDRF, ANP, and prostaglandins. Thus, an imbalance of these opposing forces, e.g., an activated renin–angiotensin system, can lead to microvascular constriction, increased inotropic state, and cardiac hypertrophy. These "adaptive" mechanisms may, in fact, increase myocardial oxygen consumption and hasten myocardial failure.

FUNCTION AND STATE OF ACTIVATION OF LOCAL MECHANISMS IN HEART FAILURE

The renin–angiotensin system: The potent vasoconstrictor peptide, angiotensin II, is produced both systemically and in local myocardial tissues by angiotensin-converting enzyme (ACE). In addition to the well-understood endocrine system, there is now ample evidence that the renin–angiotensin system exists in local tissues, e.g., blood vessels, heart, and kidney.

ACE is widely distributed in many tissues. It is present in the endothelium of all blood vessels. Indeed, high concentrations of ACE have been detected in the aorta, large and small arteries, and in the microvasculature. Further, ACE is present in the myocardium, particularly in the endocardium, as well as in the capillaries.[3] Recent data also suggest that the myocyte may contain lower levels of ACE. Figure 2 describes the current understanding of intracardiac angiotensin II production and action. In the microvasculature, where there is an abundance of ACE present over a large surface area, angiotensin I is converted to angiotensin II, which can then diffuse into the myocardium, activating receptors on the myocyte and leading to increased contractility or growth (Table II). Angiotensin II can also activate receptors on sympathetic nerve endings, facilitating release of norepinephrine, and increasing sympathetic activation. There is also recent evidence that angiotensin I can be converted to angiotensin II through enzymes within the heart, either ACE or an enzyme called angiotensin convertase, which has been shown to be 100% homologous to mast cell chymase.[4]

TABLE II Potential Contributions of the Cardiac Renin–Angiotensin System to the Pathophysiology of Heart Failure

Potential Tissue Effect	Pathophysiologic Consequences
Direct cellular angiotensin II effects	Positive inotropic effect Diastolic dysfunction
Facilitate adrenergic state	Positive inotropic effect Arrhythmia induction
Coronary artery vasoconstriction	Subendocardial ischemia
Proto-oncogene expression	Cardiac hypertrophy and remodeling Interstitial collagen deposition

Adapted from *Circ Res.*[6]

Evidence shows that the cardiac renin–angiotensin system is activated in cardiac remodeling and may play an important role in this process. The activation of the cardiac renin–angiotensin system in hypertrophied hearts, which are undergoing remodeling, has been demonstrated in rats with aortic banding. ACE activity and angiotensin II formation were greater in pressure overloaded left ventricular hypertrophy than in control hearts[5] (Figure 3). This activation is due to the induction of gene expression, as demonstrated by increased ACE messenger RNA (mRNA) levels in hypertrophied hearts in comparison to control. This increase in ACE mRNA is probably due to the increase in wall tension during the development of pressure overload. The consequent increase in angiotensin II production plays a role in the development of cardiac hypertrophy and the production of the pathophysiologic characteristics of cardiac hypertrophy. For example, when angiotensin I was given to the Langendorff preparation of the hypertrophied heart, there was a marked isovolumic increase in left ventricular end-diastolic pressure in comparison with control, suggesting that angiotensin causes diastolic stiffness, independent of venous effects. Further, in cultured cells, angiotensin II stimulates the expression of proto-oncogenes (e.g., c-*fos* mRNA) and autocrine growth factors, which cause the cells to undergo hypertro-

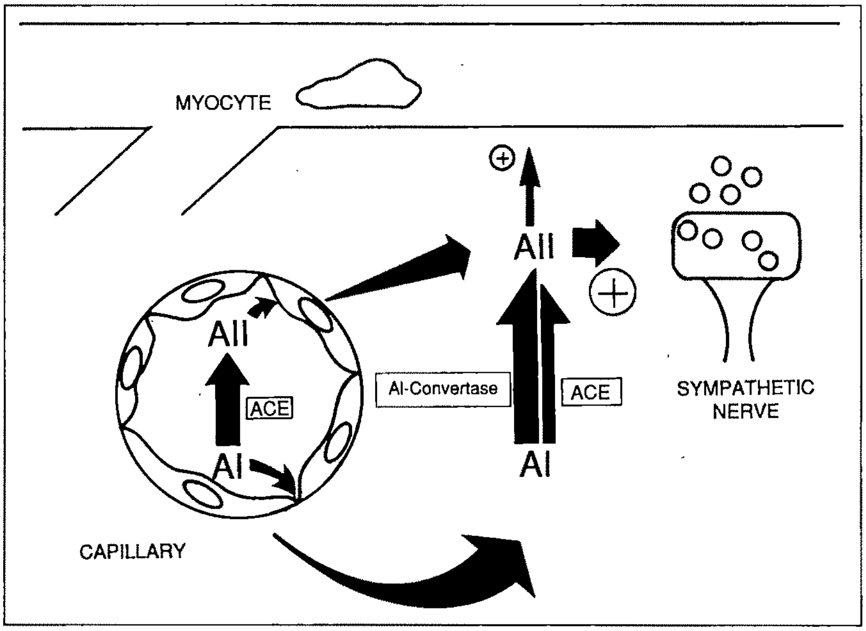

FIGURE 2. Schematic representation of the actions of angiotensin II (AII) produced by local conversion. AI = angiotensin; ACE = angiotensin-converting enzyme.

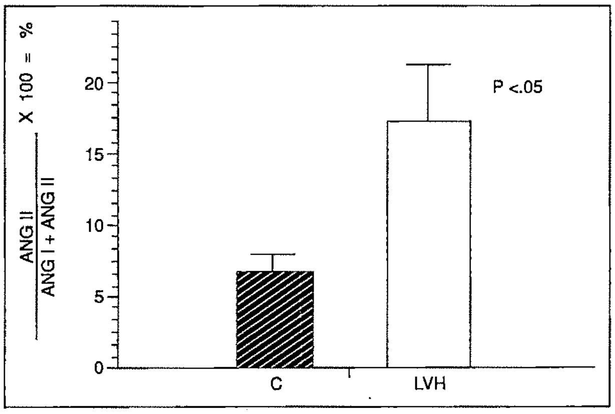

FIGURE 3. Angiotensin I (ANG I) conversion rate in isolated rat hearts with left ventricular hypertrophy (LVH). ANG II = angiotensin II; C = control.

phy. It seems that the local renin–angiotensin systems, activated during pressure overload, have an important role in the increased production of angiotensin II within the myocardium. This produces changes in the contractile state of the heart and leads to remodeling of the heart in the long term, in order to compensate for the increased wall pressure.

This system is also activated during cardiac remodeling that results in chronic heart failure, as shown in rats with compensated experimental heart failure induced by coronary artery ligation. In the compensated heart failure animals, plasma renin concentration and serum ACE activities were not elevated; however, ventricular ACE activity increased approximately 2–3-fold in chronic heart failure rats compared with control animals, a difference that was statistically significant. A positive correlation existed between the degree of ventricular dilation and the level of ventricular ACE activity (Figure 4). No such relation was observed between ventricular size and serum ACE or noncardiac tissue ACE activities.[6] Taken together, we hypothesized that increased wall stress (ventricular dilation) stimulates the induction of ACE gene expression, increasing ACE activity and the production of angiotensin II, which will then play a role in the local compensation. Therefore, it appears that during the compensated state, when the endocrine system is not activated or slightly activated, the local system is activated and that this system is important for the functional and structural adaptation of the myocardium and for transition to overt heart failure and the consequent maladaptation.

Endothelin: The peptide endothelin is an element of another local system, present in the blood vessels of the microvasculature and the epicardial arteries. It is a potent vasoconstrictor composed of 21 amino acids, released by the endothelium in response to changes in blood flow and a number of agonists, and is known to be elevated in plasma in experimental and human heart failure.[7] Recent work from Burnett's lab (Margulies et al[8]) has shown that in the ventricular-paced model of congestive heart failure there was a 2-fold elevation of circulating endothelin in comparison with normal control animals that correlated well with known physiologic markers of congestive heart failure. When endothelin is administered systemically, it produces increased systemic vascular resistance and mean arterial pressure but reduces cardiac output in a fashion similar to angiotensin II. This requires high levels of endothelin in the systemic circulation, and it has been proposed that these are not present during chronic compensated heart failure, although there is a mild activation of endothelin, particularly within the blood vessels of the microcirculation. Under these circumstances, endothelin is a vasoconstrictor within the heart and can act as a positive inotropic agent, compensating for the failing myocardium. As with angiotensin II, it can also act as a growth-promoting factor that plays a local modulating compensatory role during chronic heart failure. Indeed, receptors for endothelin have been identified in cultures of rat cardiac myocytes,[9] and Kelly and coworkers[10] have shown that there is a positive inotropic effect when endothelin is added to cultured cardiac myocytes. The actions of endothelin and angiotensin II illustrate an interesting phenomenon: that a vasoconstrictive substance, when activated systemically, primarily impedes cardiac output but when acti-

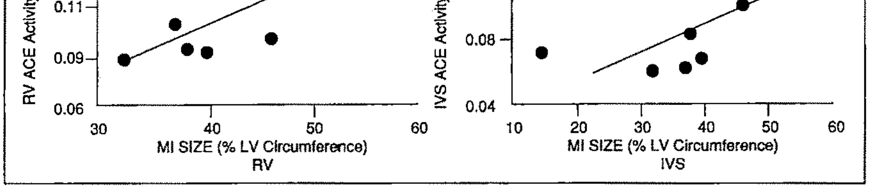

FIGURE 4. Correlation between histopathologic size of myocardial infarction (MI) and the level of right ventricular (RV) angiotensin-converting enzyme (ACE) activity. IVS = interventricular septum; LV = left ventricular. (Adapted with permission from *Circ Res*.[6])

vated locally exerts a positive inotropic effect. In addition, endothelin may stimulate renin and aldosterone release and enhance the conversion of angiotensin I to angiotensin II. It also has mitogenic potential that may contribute to structural remodeling in the cardiovascular system by stimulation of the proliferation of vascular smooth muscle cells and fibroblasts.

Endothelium-derived relaxing factor: EDRF is also synthesized in the microvasculature of the heart and is a vasorelaxant that modulates contractility and can inhibit cell growth via cyclic guanosine monophosphate (GMP) production. Therefore, it must act by antagonizing the effects of endothelin and angiotensin II. In heart failure, systemic and local blood vessel EDRF production is impaired, so it is unable to modulate fully the increased local production of angiotensin II. A study by Treasure and coworkers[11] investigated EDRF release in the coronary microcirculation in patients with dilated cardiomyopathy and found that there was a marked impairment of endothelium-dependent relaxation in response to acetylcholine in comparison to normal control patients, whereas the response to the smooth muscle relaxant adenosine was not significantly different. This suggests that EDRF production is impaired in heart failure, especially by the myocardial microvasculature, and consequently this may influence blood flow as well as contractility and structure. In other words, reduced EDRF in the setting of increased local angiotensin II and endothelin should result in reduced microvascular flow and increased cardiac remodeling.

Atrial natriuretic peptide: ANP is known to be expressed in the atrium; it is a vasorelaxant and a natriuretic substance when discharged into the circulation. It has a negative inotropic effect and is also a growth inhibitor.[12] It is interesting to note that during heart failure, ANP is not only expressed in the atrium, but also in the ventricle. It has been shown in both animals and in humans that the ventricular myocardium expresses ANP and recaptures a fetal genetic program.[13] This locally produced ANP will exert a local action in the failing ventricular myocardium.

It is easy to see that there is a new paradigm emerging in heart failure, involving a very complex series of events and interactions that have to be understood in addition to the systemic compensatory mechanisms. There are many events within, and interactions between, the different cell types (endothelium, myocytes, fibroblasts) within the myocardium that are activated to compensate for the failing heart (Figure 5). The outcome, even without intercurrent ischemia, is ventricular remodeling leading to ventricular dilation and, eventually, overt heart failure.

Cytokine involvement of the inflammatory system: It has been suggested that the inflammatory system may also play a role in the transition to heart failure, whether through a direct effect on the myocardium or through endothelial cell intermediaries is unknown. Thus, circulating cells may

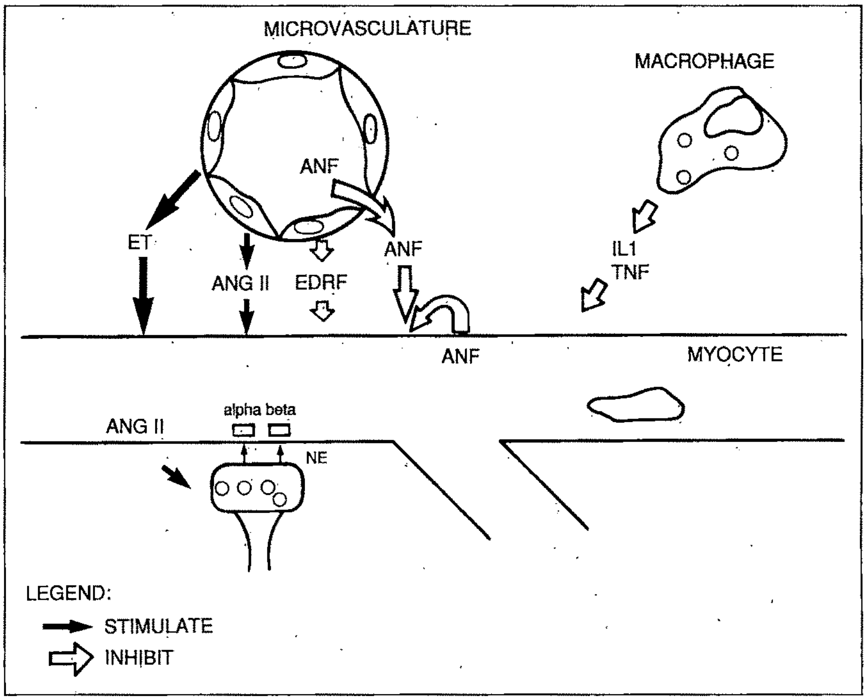

FIGURE 5. Schematic representation of crosstalk between microvasculature, macrophages, and myocytes. ANF = atrial natriuretic peptide; ANG II = angiotensin II; EDRF = endothelium-derived relaxing factor; ET = endothelin; IL1 = interleukin-1; NE = norepinephrine; TNF = tumor necrosis factor.

also play a role in heart failure. It is well known that during post-ischemic reperfusion, leukocytes become activated, enter the myocardium, and release substances such as superoxide free radicals that may further injure the myocardium. Additionally, these leukocytes express adhesive molecules and release cytokines that may also affect myocardial function and structure. Recently, Packer's group (Levine et al[14]) investigated the potential role of tumor necrosis factor (cachectin) in cardiac cachexia. Serum levels of tumor necrosis factor were higher in patients with heart failure than in healthy control subjects, and the patients with high levels of tumor necrosis factor were more cachectic and had more advanced heart failure. Tumor necrosis factor activation in heart failure is not due to impairment of clearance, secondary to renal vasoconstriction, because in chronic renal failure there is no increase in tumor necrosis factor. Tumor necrosis factor causes weight loss and negative protein balance and is thus thought to be responsible for the cachexia of severe heart failure.[14] However, tumor necrosis factor has many other actions, e.g., if it is activated within the myocardium it may have a negative inotropic effect, and it increases capillary permeability, possibly promoting edema formation.

In addition to tumor necrosis factor, interleukin-1, another cytokine released by immune cells, has negative inotropic effects on cardiac myocytes. A recent study utilized cultured myocytes and showed that interleukin-1 exerted a negative inotropic influence on β-adrenergic stimulated contractility.[15] It would be valuable to examine the cellular effect of this cytokine on failing adult myocytes, either in vitro or in an animal model of congestive heart failure. The association between cytokines of immune and heart failure origin is particularly intriguing, because the increase in tumor necrosis factor in heart failure patients correlated with activation of the renin–angiotensin system. Investigation of the molecular basis for the relation between cytokines of immune origin and local or systemic activation of angiotensin may provide information about the mechanism underlying the therapeutic effects of ACE inhibitors, and thus about the cellular role of angiotensin II in the transition to overt heart failure.

CONCLUSION

The complex paradigm proposed in this review is summarized in Figure 5. Greater understanding of these local mechanisms in the future may lead to drug therapies that can selectively block each of these mechanisms and prevent the progression from compensation to overt heart failure. In summary, myocytes interact with microvasculature, fibroblasts, connective tissue, and circulating cells such as macrophages. There is crosstalk between all of these different cells, i.e., they modulate each others' functions, with a net functional effect in the heart. In the microvasculature, endothelin and angiotensin II produced by the blood vessels are positive inotropic agents and growth promoters involved in cardiac remodeling. EDRF and ANP released from the capillary lumen into the interstitium may act as negative inotropic agents and growth inhibitors. In fact, ANP is also produced by the myocardium itself and is thought to be very important in modulation of cardiac function and structure. In addition, angiotensin II affects sympathetic neurons, further influencing cardiac function and structure.

After myocardial injury, there is an acute systemic endocrine response that usually returns to normal as cardiac compensation is achieved. There is now evidence of tissue autocrine/paracrine mechanisms that become activated during the compensated phase. These elicit local responses, which are initially adaptive but which can become maladaptive. When they become maladaptive, they can induce further myocardial injury. This vicious cycle can eventually result in decompensation and overt heart failure.

This review is a summary of a compilation of many observations leading to a new hypothesis that awaits further investigation. The possibility of much exciting research has opened for both basic scientists and clinicians to investigate the cellular processes in the myocardium that play important physiologic roles in the transition to heart failure.

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Effects of Angiotensin-Converting Enzyme Inhibitors on Tissue Renin–Angiotensin Systems

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The renin–angiotensin system (RAS) plays a major role in the control of blood pressure and cardiovascular homeostasis and is involved in the pathogenesis of a number of cardiovascular disorders. The efficacy of angiotensin-converting enzyme (ACE) inhibitors in the treatment of hypertension and congestive heart failure has led to the widespread clinical use of ACE inhibitors in primary or secondary prevention of heart disease. The demonstration of the expression of the components of the RAS in several extrarenal tissues, as well as local generation of angiotensin II, has confirmed the existence of a tissue RAS that may serve organ-specific functions and act independently from the plasma RAS. The concept of paracrine/autocrine functions of the local RAS has changed our understanding of the functions of the RAS and suggests that tissue ACE inhibition may be of greater importance than inhibition of circulating ACE in the treatment of congestive heart failure and other cardiovascular disorders. Whereas the circulating endocrine RAS appears to be responsible for mediation of acute effects, the tissue RAS seems to be involved in more chronic situations, such as secondary structural changes of the cardiovascular system, and therefore could contribute to the pathogenesis of hypertension as well as other cardiovascular disorders, such as cardiac hypertrophy, coronary artery disease, and atherosclerosis. Several experimental and clinical findings suggest that reversal of cardiovascular structural changes secondary to cardiovascular disease and enhancement of renal sodium excretion by ACE inhibitors are important long-term antihypertensive actions possibly mediated by inhibition of the tissue RAS.

(Am J Cardiol 1992;70:12C–19C)

Angiotensin I converting enzyme (enzyme classification, EC 3.4.15.1) is a metallopeptidase containing a zinc ion in its active site.[1] It is identical to kininase II, which is responsible for the breakdown of bradykinin. Angiotensin-converting enzyme (ACE) inhibitors interact with the zinc atom and thus interfere with the catalytic site.[2] Shortly after the introduction of ACE inhibitors into antihypertensive therapy, it became apparent that the interference of ACE inhibitors with the circulating renin–angiotensin system (RAS) alone could not satisfactorily explain their mechanism of action. Studies that demonstrated a lack of correlation between the hypotensive effects of the ACE inhibitors and pretreatment plasma renin activities,[3] as well as persistent renin activity in plasma of anephric humans,[4] were preceded by reports on the presence of the components of the RAS in a number of tissues, using biochemical measurements or systems.[5–8] The postulation of a functional tissue RAS implied a possible role for these systems in the regulation of blood pressure and cardiovascular homeostasis.

The existence of local tissue RAS, long suspected based on these biochemical data, has now been confirmed in brain, heart, kidney, adrenal glands, and the vasculature by the demonstration of expression of the genes for renin,[9–11] angiotensinogen,[12–14] and converting enzyme,[15] proving de novo synthesis. In addition, ligand-binding studies[16,17] and the recent cloning of the angiotensin I receptor together with the development of angiotensin II receptor antagonists have made it possible to analyze the distribution and regulation of angiotensin receptors in a number of target organs[18,19] and indicate that angiotensin exerts organ-specific functions. The concept of paracrine/autocrine functions of the RAS in the regulation of cardiovascular function postulates that locally produced angiotensin II influences local tissue function and structure, such as vascular tone, cardiac contractility and mass, renal hemodynamics, and sodium handling. This has been confirmed by studies showing the beneficial effects of ACE

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inhibitors with respect to their antihypertensive, antiproliferative and cardioprotective impact, which are apparently independent of ACE inhibition in plasma.[20] Although it remains to be seen to what extent the efficacy of ACE inhibitors may be due to their actions on the metabolism of other vasoactive peptides such as bradykinin, prostacyclin, or prostaglandins, the dissociation between the time course of ACE inhibition in plasma and the decrease of blood pressure as well as their antihypertensive action, irrespective of plasma renin activity, point to a direct involvement of local tissue RAS.

Differentially regulated gene expression of certain tissue RAS[21] has been demonstrated in several experimental animal models of hypertension, such as spontaneously hypertensive rats[22] and rats with experimentally induced hypertension[23] or cardiac hypertrophy.[12] The coincidence of the expansion of basic science with the availability of clinically effective ACE inhibitors for experimental and clinical studies has greatly enlarged our knowledge and understanding of the molecular mechanisms of the RAS under pathophysiologic conditions, such as hypertension and cardiovascular disease. Experimental data indicate that ACE inhibitors are able to inhibit tissue ACE and that tissue bioavailability seems to be the major determinant of their therapeutic effects.[24,25]

CONVERTING ENZYME INHIBITORS AND THE BRAIN

The functional significance of a local brain RAS for central cardiovascular regulation was first suggested more than 2 decades ago by Ganten et al,[6,26,27] who identified angiotensin-forming enzyme activity in the brain. Together with the finding that angiotensinogen, the precursor of angiotensin I, is generated in the brain and that its synthesis could be localized in both neural and glial cells, there was considerable evidence that angiotensin II may be formed centrally.[28,29] This was soon confirmed by the demonstration of the expression of angiotensinogen as well as renin mRNA using in situ hybridization techniques in the brain of mouse and rat.[30,31] In addition, Mendelsohn et al[32] and Tsutsumi and Saavedra[33] demonstrated the presence of angiotensin II receptors in the brain.

It was postulated that angiotensin II generated in the brain may be involved in the central control of volume homeostasis,[34,35] including the regulation of drinking behavior and salt appetite, and that it has an influence on the release of pituitary hormones such as vasopressin, adrenocorticotropic hormone, and prolactin and the modulation of central sympathetic nervous tone,[36–39] thus acting as a neurohormone or neurotransmitter.[8]

Although the exact mechanism of angiotensin II synthesis and regulation in the brain remains unclear, several experimental studies employing the intracerebral administration of ACE inhibitors have clearly demonstrated a functional role of the brain RAS. Unger et al[40] reported that intracerebroventricular application of ACE inhibitors in spontaneously hypertensive rats was associated with a sustained reduction of blood pressure without affecting the peripheral parameters of the RAS. This finding strongly suggested that a stimulated brain RAS may contribute to the pathogenesis of hypertension in spontaneously hypertensive rats.[40] This was confirmed by the demonstration that intracerebroventricular administration of ACE inhibitors in spontaneously hypertensive rats lowered blood pressure to a larger extent than when given intravenously.[41,42] In addition, the antihypertensive effect of low-dose intracerebroventricular infusion of ACE inhibitors was shown to be associated with a marked inhibition of ACE activity in the brain but not in the periphery.[40] In this experiment a correlation of the hypotensive effect with an ACE inhibitor-induced accumulation of cerebral bradykinin could be clearly ruled out, since bradykinin, unlike its vasodilatory effect in the periphery, causes an increase in blood pressure when acting on receptors within the central nervous system.[43] A markedly improved baroreceptor function and decrease in vascular reactivity following chronic intracerebroventricular treatment with ACE inhibitors in spontaneously hypertensive rats[44] also points to an involvement of the brain RAS in the regulation of vascular tone in the periphery, thus influencing peripheral resistance and tissue perfusion. In addition, it could be shown that intracerebroventricular infusion of the angiotensin II receptor antagonist saralasin in spontaneously hypertensive rats also lowered blood pressure, verifying that an inhibition of angiotensin action was the cause for the effects of ACE inhibition.[45,46] This led to the conclusion that inhibition of an overactive brain RAS in spontaneously hypertensive rats lowered blood pressure independently from the plasma RAS.

CONVERTING ENZYME INHIBITORS AND THE HEART

Soon after the introduction of ACE inhibitors into antihypertensive therapy, it was noted that inhibition of angiotensin II generation was particularly effective not only in the treatment of hypertension, but also in the treatment of chronic heart failure.[6,47] Inhibition of angiotensin II following ACE administration results not only in vasodilation, but also in redistribution of regional blood flow in favor of vital organs, such as kidney, brain, and heart, leading to an increased coronary blood flow despite a reduced systemic blood pressure.[48] Another unique feature of ACE inhibition was the regression of myocardial hypertrophy,[49,50] which could not be solely attributed to a normalization of blood pressure. These findings eventually led to the debate as to whether the beneficial effects are due to inhibition of circulating or locally generated angiotensin II.

Several studies employing molecular biology techniques clearly demonstrated local production of angiotensinogen,[13,14,51] renin,[21,52,53] and ACE[15] mRNA in the heart, proving the existence of a cardiac RAS. In addition, angiotensin binding sites were detected in rat as well as in human myocardium.[54,56] To distinguish between direct and indirect inotropic effects of angiotensin II, such as influences of the sympathetic nervous system, investigations were performed with pharmacologic agents such as β-adrenergic blockers[57,58] and with cardiac denervation,[56,59] and on isolated cardiomyocyte preparations. These experiments demonstrated that angiotensin II acts as a positive inotropic agent.[57] At the cellular level, the inotropic, direct effects of angiotensin II are apparently mediated by their influence on calcium homeostasis and transmembranous conductance.[60,61] In addition, it has been shown that ACE inhibitors not only normalize left ventricular mass, but also the changes of the isomyosin pattern[62] and that they are capable of preventing myointimal proliferation in response to endothelial injury.[63] This provides evidence for a role of angiotensin II in the pathogenesis of hypertrophic changes in the heart, although a direct involvement in the development of cardiac hypertrophy is still controversial. The question that remains is to what extent the prevention or reduction of cardiac hypertrophy in animals[64,65] and humans[66,67] following ACE blockade depends on changes in systemic hemodynamics. However, a recent study[68] with a nonantihypertensive dose of ACE inhibition resulted in a prevention and reduction of hypertrophy in rats subjected to aortic banding.

The possible role of angiotensin II as a growth factor has been confirmed recently using cultured cells. Angiotensin II increases, via protein kinase C, the expression of the nuclear proto-oncogenes c-*fos*, c-*myc*, c-*jun* and of the platelet-derived growth factor (A-chain). This is thought to play an important role in the regulation of cell proliferation in cardiomyocytes.[69,70]

The important pathophysiologic role of the tissue RAS is emphasized by the beneficial effect of ACE inhibition in cardiac diseases associated with chronic hypertension, such as coronary heart disease, acute myocardial ischemia, and adaptive processes after infarction. Clinical studies demonstrating antianginal effects of ACE inhibition[71] as well as reports that ACE inhibitors attenuate reperfusion injury and improve myocardial function while reducing arrhythmogenic potential[72–74] have focused particular interest on cardioprotective effects of ACE inhibitors not only in prevention and reduction of cardiac hypertrophy, but also on the effects of ACE inhibitors on the consequences of myocardial reperfusion after restoration of coronary blood flow by thrombolytic substances in the acutely ischemic or infarcted myocardium. Experiments on isolated heart preparations[73] allowing detailed studies of intracardiac hormonal systems such as the RAS demonstrated the prevention of postischemic arrhythmias as well as improvement of coronary flow and ventricular function by administration of ACE inhibitors. Data demonstrating a reduction in infarction size after coronary artery ligation in dogs treated with ACE inhibitors[75] show that the area at risk and the infarcted region were smaller than expected following ACE inhibitor administration. However, these effects may not be due solely to an interaction with the cardiac RAS, but also to a prolonged action of bradykinin.

The interaction of angiotensin II with other hormonal systems is an intriguing aspect of the physiology of the heart. It is known that angiotensin II increases the generation of prostaglandins, possibly via the kinin system.[76,77] The modulatory role of prostaglandins in cardiovascular disease, however, has not been defined clearly. In addition, it is unlikely that the beneficial effects of converting enzyme inhibitors are exclusively due to their action on the RAS, since these substances also interfere with bradykinin metabolism. Several investigators have addressed the question whether bradykinin contributes to some of the cardioprotective effects of ACE inhibition.[78,79] In isolated heart preparations, under ischemic conditions, exogenous bradykinin has been shown to mimic some of the antiarrhythmogenic properties of ACE inhibitors.[80] Studies on the physiology of bradykinin metabolism were complicated by its very short half-life. However, the recent availability of bradykinin antagonists has made it possible to study its effects in vivo. Martorana et al[81] demonstrated that infusion of a bradykinin antagonist could attenuate the beneficial effects of ACE inhibitors to a large extent, confirming that the prolonged action of bradykinin is also involved in the cardioprotective effects of ACE inhibition. In addition, they may also participate in the improvement of coronary flow, since they have been shown to enhance the production of prostaglandins and endothelium-derived relaxing factor.[82,83]

Several studies demonstrated that ACE inhibitors reduce the incidence and mean duration of malignant arrhythmias.[73,81,84–86] This effect could be abolished by angiotensin II and bradykinin antagonists. In addition, the observed reduction of norepinephrine overflow in ischemic hearts may result from an interaction of angiotensin II with the sympathetic nervous system.

An additional pathophysiologic aspect of the postischemic phase of acute ischemia is the "stunning" of the myocardium. This phenomenon is defined as a transient contractile dysfunction of the viable myocardium in the peri-infarction area salvaged by reperfusion. The morphologic changes occur in the extracellular collagen matrix connecting the cardiac myocytes, which are not damaged. Reperfusion has been shown to cause a number of deleterious effects, one of which is the generation of reactive oxygen free radicals, increasingly produced during reintroduction of molecular oxygen to the previously ischemic area, which finally leads to membrane damage. The influence on the preservation of the intercellular collagen may be caused by the free radical scavenging properties of the sulfhydryl group of some converting enzyme inhibitors.[74]

The term "ventricular remodeling" refers to the pathomorphologic changes after myocardial infarction, which are characterized by a gradual stretching and thinning of the ventricular wall (myocyte slippage) with progressive enlargement of the ventricle and loss of contractile capacity.[87,88] This process eventually leads to progressive myocardial fibrosis[89,90] and to chronic heart failure. The dilation is not necessarily associated with an increase of filling pressure, but frequently accompanied by a shift to the right of the ventricular pressure–volume curve characteristic of a volume overload hypertrophy.[91,92]

The beneficial effects of ACE inhibition consist of a decrease or prevention of ventricular remodeling. Patients receiving ACE inhibitors at an early, asymptomatic stage of left ventricular systolic dysfunction were less likely to develop an increase in end-diastolic volume and showed lower left ventricular filling pressures with an increased ejection fraction and an improved exercise tolerance.[93–95]

Chronic treatment with ACE inhibitors reduced the mortality in patients with heart failure[96] and, in contrast to other vasodilators, their cardioprotective effects may be produced by their direct influence on the local tissue RAS.

CONVERTING ENZYME INHIBITORS AND THE VASCULATURE

The fact that ACE inhibitors are dramatically effective in so-called normal or low renin hypertension has clearly demonstrated that high circulating levels of angiotensin II are not essential for the hypertensive effects of inhibitors of the RAS. It has been argued that vascular renin and subsequent local generation of vascular angiotensin II might be more important than circulating angiotensin II. Evidence for this was largely provided by studies with spontaneously hypertensive rats, a model of genetic hypertension and normal plasma renin activity. It was demonstrated that arterial wall renin concentrations in spontaneously hypertensive rats are elevated.[97,98] In addition, vascular renin concentrations persisted following bilateral nephrectomy, which was associated with a decline of plasma renin activity.[98,99] Further studies measuring ACE activity in aortic, brachial, and mesenteric vessels of spontaneously hypertensive rats revealed higher ACE activity compared with normotensive Wistar-Kyoto rats, whereas plasma ACE activity in spontaneously hypertensive rats was lower,[100] providing evidence that inhibition of vascular ACE may be of therapeutic importance.

Evidence for the existence of all components of the RAS in the vasculature has been produced by several biochemical, immunohistochemical, and molecular biology studies that revealed renin,[101] angiotensinogen, and ACE[102] in the vasculature. Angiotensinogen mRNA was detected in the media and adventitia of the rat aorta.[103,104] ACE mRNA was found in human aorta and venous vessels.[15] However, because of its direct exposure to the circulation, it has been very difficult to differentiate local and systemic effects in vivo. The components of the RAS may be taken up from the plasma or locally synthesized.[105,106] The employment of cell culture or isolated vessel preparations allows specific study of the vascular RAS independent of the circulating RAS. Tang et al[107] demonstrated that angiotensin I, angiotensin II, and angiotensin III are secreted from cultured endothelial cells and that secretion is stimulated by the β-adrenergic agonist isoproterenol. In similar experimental settings it has also been shown that cultured aortic smooth muscle cells were able to synthesize renin[108] and to convert angiotensin I to angiotensin II.[109] These findings support the hypothesis of an autocrine/paracrine regulated system, which may be involved in the regulation of blood vessel tone as well as in the development of adaptive changes secondary to hypertension. In isolated arteries from dogs, contraction was induced following administration of angiotensin I. This effect was suppressed by ACE inhibitors or an angiotensin II antagonist,[110] providing evidence for a RAS-specific receptor-mediated mechanism. This receptor-mediated activation of vascular smooth muscle cells by angiotensin II leads to the formation of 2 second messengers, inositol triphosphate (which rapidly mobilizes free calcium, initiating the calcium-dependent phosphorylation of the myosin light chain, resulting in cellular contraction) and diacylglycerol, which activates protein kinase C, mediating tonic effects of vascular smooth muscle cells.[109]

Chronic hypertension induces a number of secondary structural changes in the vascular wall, leading to an enhanced vasoconstrictor response to vasoactive substances such as angiotensin II.[111] Locally formed angiotensin II contributes to the regulation of vascular function not only via short-term effects, such as direct contraction and facilitation of sympathetic transmission, but also via long-term effects that are mediated by its growth-promoting and mitogenic properties.[112–114] Angiotensin II has been shown to influence the expression of the platelet-derived growth factor (A-chain)[103] as well as the expression of the protooncogenes *c-fos* and *c-myc* in cultured vascular smooth muscle cells, which in turn exert mitogenic effects by inducing DNA transcription.[103] These effects can be blocked by saralasin. In addition, angiotensin II itself is involved in the pathogenesis of adaptive changes of the vasculature, since it could be shown that smooth muscle cells in culture respond with hypertrophy following administration of angiotensin II.[115] In this context it is of interest that angiotensin II has been reported to bind intracellularly to the nucleus.[116] Further, it has been shown to stimulate RNA synthesis in isolated hepatic nuclei,[117] although exact molecular mechanisms remain to be investigated. Further evidence for a specific role of the RAS in structural changes in vivo was provided by Powell et al,[63] who demonstrated that hypertrophy of the vessel wall secondary to an experimental lesion of the carotid artery in rats was prevented by treatment with ACE inhibitors but not by administration of other antihypertensive agents such as β-receptor blockers.

Another early pathologic alteration of arteries is the formation of atheromatous plaques, especially in the presence of hyperlipidemia. Recently, Chobanian et al[118] reported that administration of ACE inhibitors resulted in reduced formation of atherosclerotic plaques in the aorta of normotensive heritable hyperlipidemic rabbits. Several other autocrine- and paracrine-acting substances are generated within the vessel wall, such as endothelin[119] or endothelium-derived relaxing factor (nitric oxide).[82] Their interactions with the RAS or other vasoactive systems and the therapeutic implications await further investigation.

OUTLOOK

Hypertension results from pathologic alterations in control systems that normally regulate blood pressure. These systems include cardiovascular, neuronal, and endocrine as well as paracrine mechanisms that interact in a complex but integrated manner to achieve blood pressure homeostasis. Besides angiotensin II, there are multiple endogenous biologically active substances participating in the regulation of these control systems. The development of ACE inhibitors has added much to the understanding of these systems due to their multiple interactions with them.

A major aspect of the investigation of the functional role of tissue RAS was the verification by molecular biologic techniques of local synthesis of the components of the RAS in several organ systems known to be involved in cardiovascular regulation. In vitro studies with isolated tissues such as vascular smooth muscle cells or cardiomyocytes demonstrated conversion of angiotensin I to angiotensin II and activation of intracellular signal transduction pathways, confirming the hypothesis of paracrine functions. The local interactions with other neurosecretory systems such as the catecholaminergic and the kinin systems represent an important aspect of the function of tissue RAS. Angiotensin II also has potent direct effects on myocardial contractility and may have deleterious effects during ischemia and reperfusion.

These findings support the view that structural changes occurring during the chronic state of hypertension such as cardiovascular hypertrophy are possibly mediated by local RAS. The physiologic significance of locally generated angiotensin II was suggested indirectly by the antihypertensive and cardioprotective effect of ACE inhibitors, which strongly supports the view that the RAS is substantially involved in the pathogenesis of cardiovascular disease. Most of the benefits of ACE inhibitors can be explained by their hemodynamic, neurohumoral, and anatomic effects. These are both systemic and local in nature and can be summarized as follows: suppression of pressor hormones; potentiation of local vasodilators such as kinins, resulting in reduction of afterload, enhanced myocardial function, and preservation of myocardial integrity; and attenuation of cardiovascular hypertrophy interrupting the vicious cycle that eventually leads to decompensated chronic heart failure.

The regulation of the genes of the RAS has been shown to be altered in several models of primary hypertension. However, the underlying mechanisms of the pathogenesis remain to be elucidated. Obvious similarities between humans and rats exist regarding blood pressure regulation, such as the RAS, based on similar or even identical structures at the molecular level. The recent introduction of transgenic techniques into cardiovascular research offers a possibility to explore further those molecular mechanisms that contribute to the origin of hypertension. The phenotype of the transgenic rat, (mRen 2)27, carrying the mouse Ren-2d gene in its genome, is characterized by a marked hypertension. Interestingly, both expression of the renin gene in the kidney as well as circulating renin levels are strongly suppressed, whereas renin expression in extrarenal tissues, such as the adrenal gland, gastrointestinal tract, thymus, and brain, is increased.[120,121] In addition, they have been shown to respond to ACE inhibitors with high sensitivity.[122] Therefore, this model of hypertension represents an excellent tool to study the functions of tissue RAS and supports a role for the renin gene as a candidate gene for hypertension. Another approach employing linkage studies with random markers allows identification of new candidate genes, which so far have not been associated with high blood pressure. Using this approach, Jacob[123] and Hilbert[124] and their colleagues recently identified 2 loci in the genome of cross-breedings between genetically hypertensive, spontaneously hypertensive rats and normotensive Wistar-Kyoto rats, which significantly correlated with the hypertensive phenotype in F2 (second-generation) cohorts. Interestingly, these genes were assigned to the rat chromosome 10 within a region that also contains the ACE gene. Although these findings do not necessarily imply a pathogenetic role for ACE, since they represent only genetic markers, they identify the ACE gene as another potential candidate gene, for which a regulatory role on angiotensin II generation in plasma as well as in tissue has been suggested by several authors.[1,125,126]

Information of these molecular studies offers new insights into complex multigenetic diseases such as primary hypertension and may help to develop new strategies for therapy and prevention.

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Ventricular Remodeling Following Myocardial Infarction

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Ventricular remodeling denotes structural changes that occur in ventricular chamber size, wall thickness, and composition following myocardial damage. Following acute coronary occlusion, there are various factors to consider at different times that may contribute to subsequent ventricular dilation. Early infarct expansion and later healing may be accompanied by compensatory hypertrophy in the noninfarcted region and progressive global dilation, that may progress long term, the major stimulus being increased wall stress. The 2 major factors influencing ventricular remodeling following myocardial infarction are infarct artery patency and the ventricular loading conditions. Thrombolytic therapy may produce coronary reperfusion and limit infarct size. Patency of the infarct-related artery may also provide later benefits for ventricular remodeling. Following infarct evolution, pharmacologic intervention provides the potential to minimize the sequelae of infarct expansion and ventricular dilation. Clinical studies indicate that treatment of symptomless left ventricular dysfunction with angiotensin-converting enzyme inhibition at ≥1 week following myocardial infarction may prevent further ventricular dilation and reduce the probability of progression to heart failure. Earlier intervention, at 24–48 hours following Q-wave myocardial infarction, is also practicable and effective. Even earlier intervention, in combination with or immediately following thrombolysis, is being assessed in other studies. The timing of treatment is of considerable importance because blockade of compensatory mechanisms activated at the time of infarction may not be desirable immediately, even though these mechanisms may be deleterious later. The results of large-scale mortality studies are awaited to indicate the benefit of this type of treatment in terms of heart failure prevention and survival long term.

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The structural and functional changes that occur in heart failure have long been studied. However, it is only relatively recently that the term "cardiac remodeling" has been introduced, as the complexity and importance of the regional and global changes in ventricular size, shape, and composition that occur in heart failure have become better understood. Cardiac or ventricular remodeling denotes structural changes that occur in ventricular chamber size, wall thickness, and composition following myocardial damage. The regional and global topographic changes that occur following myocardial infarction have been the subject of most studies on this subject, but it is also relevant to consider myocardial changes that occur in other forms of heart failure with pressure or volume overload.

Whatever the underlying cause of heart failure, there is commonly a prolonged period prior to the occurrence of clinically manifest congestive heart failure (CHF) during which ventricular remodeling occurs, initially as an adaptive compensatory process with varying degrees of ventricular dilation and hypertrophy, but leading to progressive ventricular dysfunction. The poor prognosis of advanced clinical CHF has recently led to consideration of earlier intervention, during the phase of symptomless ventricular dysfunction, and treatment directed at modifying the process of ventricular remodeling.

Infarct expansion and healing: At different times following acute coronary occlusion in the clinical setting, there are various factors to consider that may contribute to subsequent ventricular dilation. Thrombolytic therapy may produce coronary reperfusion and limit infarct size. Early infarct expansion and later healing may be accompanied by compensatory hypertrophy in the noninfarcted region and progressive global dilation, which may

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progress long term, the major stimulus being increased wall stress.

A sequential 2-dimensional echocardiographic study of patients after acute transmural myocardial infarction demonstrated disproportionate dilation and transmural thinning of the infarcted zone in 8 of the 28 patients studied.[1] This regional expansion was first observed as early as 3 days after infarction and was progressive during the 2 weeks of study. Infarct segment length increased 50%, producing a total left ventricular circumferential dilation of 25%. Patients showing infarct expansion all had anterior infarcts and significantly greater 8-week mortality compared with the patients without expansion.

A distinction is required between infarct expansion and extension, i.e., between disproportionate dilation and thinning of the area of infarction not explained by additional or new myocardial necrosis.[2] Infarct extension appears to be a much less frequent event than expansion and generally will not compromise cardiac function further.[2] Infarct expansion can mimic or possibly cause extension and commonly worsens cardiac function through ventricular dilation.

Various cellular mechanisms for infarct expansion have been suggested, including myocyte necrosis and rupture, reduction in intercellular space, and stretching or slippage of myocytes.[3] Detailed histologic study of rat hearts with infarct expansion, complemented by study of human hearts, indicates that rearrangement of groups or bundles of myocytes with a decreased number of cells across the wall accounts for most of the wall thinning in the infarct zone and all the thinning of noninfarcted regions.[3] In noninfarcted regions, cell slippage accounts for wall thinning, whereas cell stretch and loss of intercellular space are confined to the infarct zone and contribute less to wall thinning than does cell slippage.

The association of infarct expansion with larger, more transmural infarcts noted experimentally has been confirmed in a large patient autopsy analysis.[4] Infarcts with greater expansion had significantly more endocardial thrombus and endocardial fibroelastosis. Left ventricular hypertrophy and increased heart weight had a significant negative correlation with infarct expansion, which occurred more frequently in left anterior descending coronary artery distribution compared with the right coronary artery. From these findings, it can be postulated that differences in the degree of normal segmental wall thickness related to radius of curvature and intramural tension explain the increased tendency for infarct expansion in the distribution of the left anterior descending coronary artery.[4] With left ventricular hypertrophy and increased wall thickness, infarcts tend to be less transmural and the apparent protection from expansion in the presence of hypertrophy may be due to relatively smaller infarct size.

TABLE I Ventricular Dilation Following Myocardial Infarction

Acute transmural infarction	
Early infarct expansion	↓
	Days
Regional ventricular dilation	↓
Continued expansion vs healing	Weeks
Increased wall stress	↓
	Months
General ventricular dilation	

Global ventricular dilation: Early infarct expansion and regional ventricular dilation after myocardial infarction may be accompanied or followed by a phase of global ventricular dilation occurring over subsequent months and involving both infarcted and noninfarcted segments (Table I). This has been demonstrated from serial 2-dimensional echocardiographic early studies in a group of patients after transmural anterior myocardial infarction.[5] Patients with early infarct expansion showed significant continuing dilation during long-term observation up to 30 months in the infarcted anterior and noninfarcted posterior segments. In contrast, the patients without initial infarct expansion showed no significant later change in anterior or posterior segment length.

Remodeling of the entire left ventricle with volume overload hypertrophy of noninfarcted segments may also occur during the early convalescent period and accompany infarct expansion. An angiographic study on admission and at 2 weeks in a group of patients with their first acute transmural anterior myocardial infarct treated successfully with thrombolytic therapy showed a significant increase in left ventricular volume over the 2-week period but a significant decrease in left ventricular filling pressure.[6] The volume increase correlated with infarct size as assessed by the extent of wall motion abnormality present acutely. Increased endocardial perimeter lengths were present in both infarcted and noninfarcted segments at 2 weeks. Lengthening of the endocardial perimeter in the ventricular wall without regional wall motion abnormality and wall thinning suggests a volume overload hypertrophy with a net increase in myocardial mass of these segments and is analogous to the

TABLE II Ventricular Remodeling Following Myocardial Infarction

Process	Intervention
Coronary occlusion	Restore infarct artery patency
Myocardial infarction	Restore infarct artery patency
Size	Optimize oxygen supply:demand
Transmural extent	Reduce regional wall stress
Reperfusion injury	Attenuate reperfusion injury
Myocardial infarct expansion Early/late	Reduce regional wall stress
Global ventricular dilation and compensatory hypertrophy	Reduce wall stress and hypertrophy
Progressive ventricular dysfunction	Ventricular unloading
Recurrent ischemia/infarction	Optimize oxygen supply:demand
Arrhythmias	
Clinical congestive heart failure	Relieve congestion Block neurohormonal activation Improve myocardial contractility

compensatory hypertrophy demonstrated early following acute myocardial infarction in experimental animal studies.[7–9] Such volume overload hypertrophy results from series addition of sarcomeres, in contrast to pressure overload hypertrophy where new myofibrils are added in parallel. It has been postulated that increased diastolic pressure and wall stress from volume overload leads to sarcomere replication in series with resultant chamber enlargement.[10] Such chamber enlargement accommodates the volume overload, returning diastolic pressure to normal. The chamber enlargement also causes an increase in systolic wall stress that results in slight wall thickening.

The demonstration of early significant left ventricular diastolic dysfunction assessed by radionuclide angiography within 24 hours of acute myocardial infarction, which occurred even in patients with preserved systolic function, further supports the suggestion that left ventricular dilation and increased diastolic wall stress act as the primary stimuli for continued ventricular remodeling.[11] An increase in wall stress in infarcted and ischemic segments has also been demonstrated in patients with coronary artery disease studied by cardiac catheterization.[12] End-systolic wall stress was increased in infarcted and ischemic segments compared with normal matched segments. Residual wall stress at the end of isovolumic relaxation was increased both in infarcted areas and in noninfarcted areas perfused by stenosed arteries. However, whereas the rate of decrease in local stress in infarcted areas paralleled the rate of decrease in pressure, in ischemic areas the rate of decrease in stress was slower. Although initial volume overload and increased wall stress may be matched by adequate hypertrophy, with the tendency to progressive dilation, eventually mismatch occurs and heart failure becomes clinically manifest.[10,13]

The pattern of left ventricular dilation following myocardial infarction can be quite variable. In a group of 57 patients with myocardial infarction, none of whom had undergone thrombolysis, radionuclide evaluation showed approximately half of the patients to have $>20\%$ increase in left ventricular end-diastolic volume index from 2 weeks to 1 year following infarction.[14] A similar study with serial evaluation of left ventricular volume changes in 50 patients who did not receive thrombolysis showed $>20\%$ increase in left ventricular end-diastolic volume from day 2 to day 10 in 11 patients, and similar left ventricular dilation from day 10 to 6 months in 10 other patients.[15] Among these 21 patients, progressive dilation with serial volume increases on ≥ 2 occasions occurred in 8 patients, all of whom had large anterior infarcts. Thus, approximately 40% of infarct survivors demonstrated significant ventricular dilation within 6 months of infarction. Progressive dilation was associated with deterioration in left ventricular function and increased 2-year mortality, in contrast to patients with dilation that stabilized, who had a better clinical outcome.

MODIFICATION OF LEFT VENTRICULAR REMODELING

Various processes may contribute to ventricular remodeling at different stages from the time of coronary occlusion until the possible development of progressive ventricular dysfunction and clinical heart failure (Table II). These processes are amenable to intervention at different times, the overall aim being to prevent significant ventricular dysfunction and heart failure and improve the long-term prognosis. The loading conditions of the ventricle and infarct artery patency are of central importance in influencing ventricular remodeling and eventual outcome.

Infarct artery patency: Infarct artery patency may confer a beneficial effect on ventricular remodeling and long-term survival through mechanisms other than early limitation of infarct size. The relation between perfusion of the infarct-related artery and changes in left ventricular volume and function during the month after a first myocardial infarct has been examined in a clinical study of 40 patients who did not receive thrombolysis.[16] Spontaneous perfusion of the infarct artery was documented at predischarge angiography and left ventricular volumes assessed from radionuclide angiography within 48 hours of infarction and at 1 month. Left ventricular dilation (>20% increase in volume) occurred in all 14 patients without perfusion of the infarct-related artery compared with only 2 of 26 with perfusion due to subtotal occlusion or collateral vessels. All 5 patients with a decrease in left ventricular volume had a perfused infarct artery. The degree of perfusion was a more important predictor of volume change than was infarct size, assessed by peak creatine kinase or electrocardiographic QRS score. Thus, perfusion of the infarct-related artery may be important in preventing continuing infarct expansion and left ventricular dilation. Reperfusion may preserve endocardial tissue, and it is also possible that reperfused infarcts with contraction band necrosis may have higher tensile strength and reduced propensity to expansion than nonperfused infarcts.[17]

A further study of the time course of left ventricular dilation after myocardial infarction that confirmed variable patterns of early, later, and progressive dilation—and showed greater dilation in those with left anterior descending coronary artery occlusion—did not show any relation of volume changes to reperfusion.[18] This was attributed to relatively late thrombolysis, with delay between onset of symptoms and reestablishment of collateral flow. Various other studies of thrombolysis and left ventricular function have clearly demonstrated benefit from myocardial reperfusion with reduced infarct size and associated improvement in regional and global ventricular function.[19-22] Reperfusion and patency of the infarct-related artery may thus determine not only a reduction in infarct size and propensity to early infarct expansion, but also possible later benefits for ventricular remodeling and long-term survival.

Pharmacologic intervention: Improved understanding of the process of ventricular remodeling and the prognostic importance of ventricular dilation following myocardial infarction[23] have led to experimental and clinical studies of pharmacologic intervention for treatment of left ventricular dysfunction in the postinfarct period. As previously mentioned, thrombolysis and other measures are of proven value in the acute phase in which the primary objective is limitation of infarct size and salvage of ischemic myocardium. Once infarct evolution has occurred, however, there is potential for intervention to minimize the sequelae of infarct expansion and ventricular dilation and thus improve the long-term prognosis.

Intravenous nitroglycerin has been shown to limit infarct size, infarct expansion, other infarct-related complications, and mortality up to 1 year.[24] The beneficial effect of nitroglycerin on limiting infarct expansion was apparent from serial echocardiographic study during the first 2–3 days, suggesting early remodeling. Decreased preload and afterload were considered important contributing factors to this, although reduced infarct size and improved collateral flow may also have played a role.

There has been considerable interest in the effects of angiotensin-converting enzyme (ACE) inhibition on left ventricular remodeling. In rats studied 3–4 months after myocardial infarction, ventricular dilation and depression of cardiac performance were demonstrated to be a function of infarct size.[25] A continuum of heart failure was observed, with progressive increase in left ventricular filling pressure and decrease in maximal forward output and ejection fraction as infarct size increased. Compensatory dilation of the left ventricle allowed preservation of forward output at any filling pressure. Infarction of moderate-to-larger size reduced overall chamber stiffness. Treatment with the ACE inhibitor captopril improved forward output and reduced ventricular dilation and the change in ventricular chamber stiffness. Longer term studies in the same model showed survival was inversely related to infarct size but improved with captopril treatment, particularly in animals with infarcts of moderate size.[26]

Clinical studies have also been carried out to study the effects of ACE inhibition following myocardial infarction. In a randomized, double-blind trial, the effects of captopril, a diuretic (furosemide), and placebo were studied in patients with asymptomatic left ventricular dysfunction (ejection fraction <45%) 1 week following Q-wave myocardial infarction.[27,28] Left ventricular volume and function were assessed at intervals during the subsequent year, using 2-dimensional echocardiography. The furosemide and placebo groups showed significant increases in ventricular volumes with stroke volume index unchanged and ejection fraction slightly reduced, whereas the captopril group showed a significant reduction in left ventricular end-systolic volume index, with stroke volume index and ejection fraction increased. At 12 months, the difference in the change in ejection fraction from baseline between the captopril and other groups was about 10%.

Another study randomized patients to captopril or placebo after a mean of 18 days following a first myocardial infarction.[29] As in the former study, no patient had overt heart failure and all had ejection fraction <45%. End-diastolic volume increased in the placebo group, during the year of treatment but not in the captopril group although there was no significant difference between the groups. Dilation was more evident in the placebo patients with an extensive wall motion abnormality or with an occluded infarct-related artery. In a subgroup of patients from this study,[30] the importance of left ventricular shape in determining exercise capacity was assessed and the interaction between left ventricular shape and captopril therapy evaluated. A greater shape distortion, indicated by increasing left ventricular sphericity was associated with increased left ventricular volumes, decreased ejection fraction, and a larger abnormally contracting segment. Left ventricular sphericity index was the only independent predictor of exercise duration in the placebo group. Placebo-treated patients in the tercile with the most spherical ventricles had the lowest exercise capacity and highest heart failure and specific activity scores. Captopril-treated patients with the same baseline distortion of left ventricular shape did not show these shape-dependent changes in functional capacity.

It has been speculated that, despite the expected decrease in equatorial wall stress with changes in radius of curvature as the dilating ventricle assumes a more spherical shape, altered myocardial fiber orientation may be associated with increased stress per myocardial fiber.[31] The motion of endocardial landmarks in a normally contracting ventricle follows a pattern maximizing systolic mechanical advantage.[32] This pattern may be changed with apical distortion, which leads to loss of the mechanical advantage of orderly contraction of myocardial segments and compromises global ventricular function more than expected from the extent of the infarct alone. These observations may explain the importance of left ventricular shape as a descriptor of left ventricular structure and function as well as outcome.

Although left ventricular dysfunction can be improved with ACE inhibition commenced ≥1 week following myocardial infarction, earlier intervention appears to provide greater benefit. In a double-blind study in patients with Q-wave myocardial infarction but without clinical heart failure, treatment with captopril or placebo was commenced 24–48 hours following the onset of symptoms.[33] During 3 months of treatment, the placebo group showed significant increases in left ventricular volumes, with ejection fraction unchanged. In contrast, the captopril group showed no change in left ventricular end-diastolic volume index and a significant reduction in left ventricular end-systolic volume index with ejection fraction increased significantly. Most of the treatment benefit was evident during the first month. Comparison of the results of this study with those from the study where treatment was commenced 1 week following myocardial infarction[27,28] indicates a greater benefit from earlier treatment.

These clinical results are somewhat at variance from those of an experimental study in rats with myocardial infarction,[34] where there was no difference in benefit when oral treatment commenced immediately, 2 hours after coronary ligation, compared with delayed treatment started at 21 days, when the animals' left ventricular performance, weight, and volumes were assessed after 4 months' treatment. Also, blockade of compensatory mechanisms activated at the time of infarction may not be desirable in the immediate postinfarct period even though these mechanisms may be deleterious later. This possibility is supported by further experimental data that indicate that captopril therapy in chronically infarcted conscious rats improved cardiac function when treatment was started after completion of the healing process, but that early treatment had an adverse effect on function.[35] When captopril was given from 1–21 days during the healing period, cardiac output with volume loading was the same as in the untreated infarct control animals, but with heart rate increased and stroke volume reduced. Although the rat model is useful for studies of left ventricular remodeling after myocardial infarction, patients with coronary artery disease may respond differently to converting enzyme inhibition. Nevertheless, the timing of this treatment is obviously important clinically. Although intervention >24 hours after infarction appears practical and beneficial, more immediate treatment, <24 hours after infarction may increase the risk of hypotension with thrombolytic treatment and possibly compromise coronary perfusion. Immediate intervention may produce blockade of mechanisms, which, although disadvantageous in the long term, are initially truly compensatory and beneficial.

The mechanism of improvement with ACE inhibition is probably related principally to the peripheral vasodilating effect and ventricular unloading and in this respect both preload and afterload reduction appear to be important.[36] There may also be additional beneficial effects on the coronary circulation,[37,38] which are advantageous for remodeling. However, while coronary hemodynamic data have suggested a balanced effect of converting enzyme inhibition on the coronary circulation, a recent clinical study in patients with heart failure and ischemia has indicated that such treatment may worsen ischemia as a result of hypotension and presumably compromised coronary perfusion.[39] Finally, converting enzyme inhibition may have an important direct effect on myocardial tissue,[40–42] preventing inappropriate growth and hypertrophy stimulated by angiotensin II and other growth factors.

REMAINING QUESTIONS

The process of left ventricular remodeling has now been extensively studied, but a number of important questions remain to be answered. Although the progression from initial compensatory hypertrophy to pathologic hypertrophy has been studied experimentally, this aspect of remodeling is not easily amenable to clinical study and remains poorly understood. Studies of laboratory models of heart failure must be complemented by clinical investigation of the role of cardiac growth and hypertrophy in heart failure for a better understanding to be obtained.

With the gradual change of the myocardial infarction paradigm during the past decade from considerations of infarct size to infarct artery patency, and further to early and late ventricular remodeling, there are now a number of therapeutic interventions that may be applied. The benefits of early and late ventricular unloading and reduced wall stress have been demonstrated in terms of improved ventricular size and function, but it remains to be determined whether this is translated into clinical benefit in terms of heart failure prevention and improved survival. Large-scale studies currently in progress should provide information on this most important aspect during the next several years.

Further clinical studies are also required to confirm the optimal timing of this type of intervention and particularly the value of treatment in combination with, or immediately after, thrombolysis. Assessment of the comparative and possibly additive effects of converting enzyme inhibition, nitrates, and β-blockade in the postinfarction period is also required.

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Prospects for Cardioreparation

Jean-Pierre Ollivier, MD, and Véronique A. Bouchet, MB, BS, BSc (Hons)

The structure of the myocardium has 2 principal components, a myocytic compartment and a nonmyocytic compartment that consists primarily of interstitial tissue. It appears that increased collagen production is mainly responsible for the functional consequences of structural remodeling. The concept of cardioreparation implies both a restoration of structural abnormalities and a return of cardiac function to or toward normal. In spontaneously hypertensive rats with left ventricular hypertrophy and adverse structural remodeling of the cardiac interstitium, angiotensin-converting enzyme inhibition has resulted in restoration of myocardial integrity and stiffness toward normal. Further research needs to be undertaken to identify the molecular mechanisms involved in the development of interstitial myocardial fibrosis, and reliable methods for assessing the interstitium and the changes that occur within it in clinical practice need to be developed.

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To date, most of the research carried out in an effort to increase the understanding of the pathogenesis of heart failure has focused on the basic underlying causes, namely, loss of contractile tissue and myocyte energy availability. It has now become apparent that additional mechanisms come into play and that the nonmyocyte compartment is involved to varying degrees during the development of cardiac failure.

The difficulty faced by physicians in understanding heart failure from a clinical perspective stems from the fact that research has centered on the areas of molecular biology and fundamental sciences. The new knowledge that has evolved has, however, led to a better understanding of the structure and function of the myocardium from which the concept of cardioreparation has evolved.

In order to explain the term "cardioreparation," functional characteristics of the myocardium must be considered. The use of the word "reparation" implies the presence of histologic lesions. The myocardium, however, is exceptional in that it is a tissue that produces mechanical energy, and structural alterations in the absence of true histologic lesions can themselves have significant consequences with respect to cardiac function. The term "reparation" in the cardiovascular context must, therefore, be extended beyond the initial histologic meaning to encompass the concept of restoring not only structure, but also myocardial function, to or toward normal.

In this review, the histologic, biologic, ultrastructural, and molecular mechanisms involved in cardioreparation will be discussed from the point of view of a clinician. The methods of assessment available currently and the therapeutic implications will be considered.

BASIC PRINCIPLES AND CURRENT KNOWLEDGE

Structure and function of the myocardial interstitium: The concept of cardioreparation is based on an understanding of the dual structure of the myocardium, which is composed of a myocytic and a nonmyocytic compartment. The latter consists primarily of interstitial tissue.

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Cardiac myocytes occupy 70–75% of the total volume of the myocardium, but account for only 33% of all cells present. Of particular importance is the fact that it is generally accepted that they are unable to undergo cell division in adult life. Although myocytes are known to have a mechanical function, their secretory role is currently little understood. There is evidence to demonstrate that myocytes undergo structural modifications in a number of pathologic states and can be viable, nonfunctional or necrotic.[1] Following myocytic necrosis, fibroblasts mediate a replacement fibrosis that restores structural integrity to the tissue. This is a histologic description and should not be confused with the concept of cardioreparation under discussion here.

The cells found in the nonmyocytic compartment of ventricular myocardium include mainly endothelial cells, vascular smooth muscle cells, and fibroblasts. Cardiac fibroblasts, but not myocytes, contain the mRNA for types I and III collagen, which are the major fibrillar collagens of the heart and circulation. Cardiac fibroblasts are also likely to produce the proteolytic enzyme collagenase, which is responsible for collagen degradation. This noncontractile myocardial compartment has been named myocardial interstitium and is functionally connected to the cytoskeleton and to the contractile apparatus of the myocyte.

The spatial configuration of collagen has been described in the animal model.[2] The collagen matrix of the myocardium forms a complex 3-dimensional structure that is made up of 3 components: (1) the epimysium, an envelope of fibers surrounding muscle, lies below the epicardium and endocardium; (2) the perimysium, an extension of the epimysium, is a weave of collagen fibers that surrounds groups of myocytes to form muscle bundles or myofibers, and strands of collagen that join adjacent weaves; and finally (3) the endomysium. Endomysial collagen fibers surround individual myocytes and form lateral cell-to-cell connections of fibrillar collagen called struts (Figure 1). These are thought to produce mechanical synchronization throughout contraction and relaxation. Similar links exist between the myocytes and the vascular bed, forming a scaffolding that plays an important role in maintaining the functional integrity of the myocardium.

The myocardial interstitium can thus be considered to be a perfect mechanical structure: due to its basic architecture of types I and III collagen, an inextensible structural continuum is formed that protects cardiac myocytes and their constituent sarcomeres from excessive degrees of stretch.[3] In addition, a protein called fibronectin binds the fibrillar matrix to the myocytes and through its specific mechanical properties contributes to the viscoelasticity of the myocardium.

The normal architecture of the fibrillar matrix ensures that collagen plays a key role in the maintenance, distribution, and storage of mechanical forces during systole and in their redistribution during ventricular relaxation.

Pathophysiology of heart failure: Cardiac disorders have in the past been characterized according to the presence or absence of fibrosis. Collagen concentration usually remains unchanged in the ventricular hypertrophy that accompanies a volume overload state such as an arteriovenous fistula or anemia, whereas an increase in collagen concentration together with remodeling of the collagen matrix of the left ventricle has been observed in various states of left ventricular pressure overload

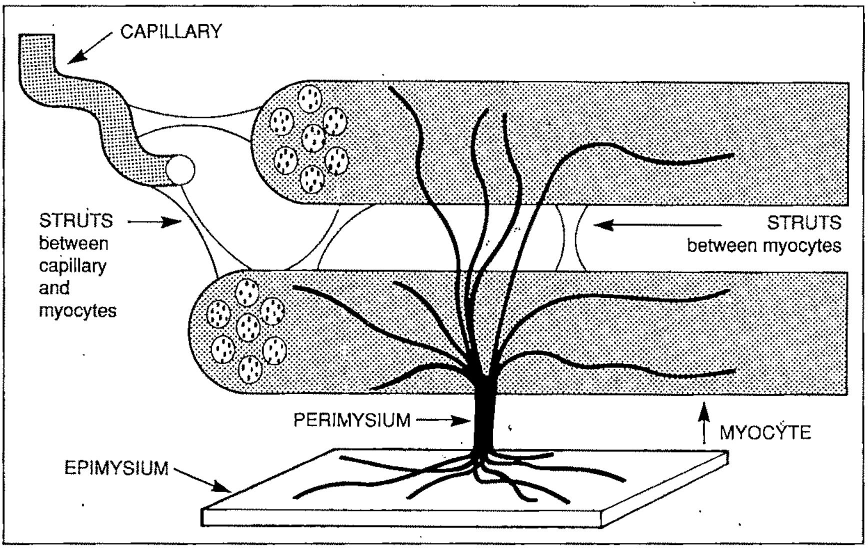

FIGURE 1. Schematic representation of the structure of the collagen matrix of the myocardium, which forms a complex 3-dimensional structure with epimysial, perimysial, and endomysial components. This "scaffolding" plays an important role in maintaining the functional integrity of the myocardium.

hypertrophy[2] (Figure 2). Clinically, such strict definitions become inappropriate during the progression of many disease states, when the etiology may be multifactorial or when general and more specific humoral mechanisms are activated to compensate for overt cardiac failure.

LEFT VENTRICULAR HYPERTROPHY: Of importance in understanding the pathophysiology of heart failure is the role played by myocardial hypertrophy. Hypertrophy would seem in some cases to be beneficial; in athletes, for example, cardiac myocyte growth is an adaptation to alterations in hemodynamic loading with little or no deleterious effects. Left ventricular hypertrophy (LVH) may in some cases be maladaptive (inadequate or excessive in relation to load) and can become pathologic when abnormalities in cardiac function become evident.

Myocardial hypertrophy appears to be quite common and frequently abnormal. When assessing the degree of LVH clinically, indices such as myocardial mass to chamber volume or wall thickness to chamber radius ratios are usually taken into account to gauge whether, under given conditions, the observed degree of hypertrophy is appropriate and fulfills its initial adaptive role of reducing ventricular wall stress and consequently myocytic work.

This approach does not take into account the actual structure of the myocardium, which cannot be precisely determined when assessing a patient; it is not possible to ascertain whether structural abnormalities such as eccentric or concentric hypertrophy are present or whether myocardial slippage has occurred. Moreover, the degree of myocytic hypertrophy and the nature and concentration of collagen cannot be determined.

Although hypertrophied myocytes are an essential component of LVH, the participation of the collagen network in the hypertrophic process is of great importance: LVH will be an adaptive process provided that the myocardium and its muscular, vascular, and connective tissue compartments remain in a state of balanced equilibrium, based on their relative proportions, structural integrity, physical arrangement, and biochemical characteristics. Pathologic hypertrophy will ensue when this intercompartmental equilibrium, which is responsible for the mechanical behavior of the myocardium and guarantees cell viability, is lost. A fine balance exists: although collagen (of which 75% in adults is type I) accounts for only 2–4% of myocardial

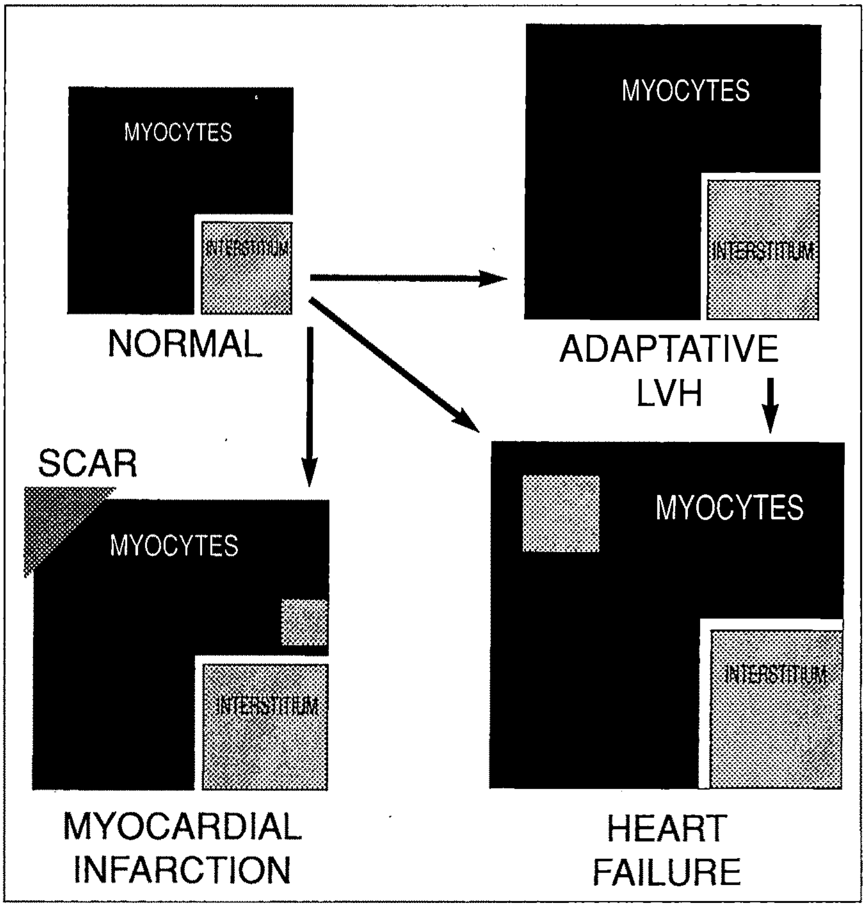

FIGURE 2. Schematic representation of the changes occurring in the myocardium in various pathologic conditions. The interstitium appears to play an important role in the structural and functional alterations observed. LVH = left ventricular hypertrophy.

weight, noticeable clinical manifestations are observed when collagen content is increased by a factor of 2.[4]

There is a wide spectrum of individual hypertrophic responses to overload. For example, myocardial mass is widely distributed in the hypertensive population and this demonstrates the complexity and variability of the underlying mechanisms. It should be noted, however, that the epidemiologic data available clearly demonstrate that LVH, which may be tolerated by hypertensive patients over the long term, represents the major risk factor associated with the subsequent development of heart failure.[5]

CARDIAC FAILURE: It is now apparent that, although decreased myocyte energy availability and later mechanical failure of the myocytic compartment play an important role in the development of heart failure, other factors are involved (Figure 3). The energetics and hemodynamics of the myocytic compartment have been studied extensively in the last 2 decades and will not be discussed further here. Present interest in the concept of cardioreparation centers on the role played by the myocardial interstitium in the development of cardiac insufficiency. When considering the pathogenic and therapeutic implications, one of the major questions under debate is whether abnormal quantitative and/or qualitative alterations represent a common finding in all cardiac disorders.

STRUCTURAL REMODELING OF THE MYOCARDIUM:The interstitial cell population does not seem to play a direct role in the mechanical properties of the ventricular myocardium, but it seems that increased collagen production by fibroblasts may be almost entirely responsible for the functional consequences of structural remodeling. In the normal state, the proportion of types I and III collagen present in the myocardium offers an optimal balance between resistance and elasticity. An increase in type I collagen leads principally to an increase in ventricular wall stiffness, the main consequence of this being impaired ventricular filling.

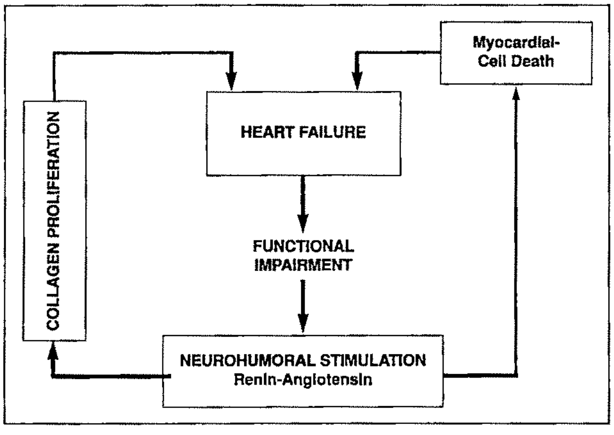

FIGURE 3. Simplified overview of adaptations to the low output state found in cardiac failure.

Myocardial collagen content can be increased in a number of ways.[4] In conditions such as experimental systemic hypertension and right ventricular pressure overload, a reactive interstitial fibrosis with accumulation of collagen in the absence of myocyte necrosis is seen. This comprises (1) interstitial fibrosis resulting from thickening of normally positioned struts (fibrillar collagen also appears in intermuscular spaces previously devoid of collagen), (2) perivascular fibrosis (accumulation of collagen within the adventitia of intramyocardial coronary arteries and arterioles), and (3) plexiform fibrosis associated with muscle fiber disarray.

In late stages of established pressure load hypertrophy, a replacement or reparative fibrosis is seen. This represents microscopic scarring following myocytic necrosis.[6] It is evident macroscopically in the case of myocardial infarction whereas it is present in a more disseminated form in other cardiac pathologic states.

The process by which the heart adapts to a sustained load during the development of cardiomyopathy of overload, originally described by Meerson as a continuous progression of 3 stages, was recently reviewed by Katz.[7] The role played by various trophic factors during this structural remodeling of the interstitium has been highlighted by Weber and Brilla.[4] Mechanisms involved include elevations in the levels of circulating angiotensin II, produced in response to an increase in arterial pressure, which may induce myocyte necrosis. This initial focal cellular necrosis causes scarring or reparative fibrosis. Also involved is increased vascular permeability, which leads to diffusion of growth factors. The last component is a cellular one, fibroblast proliferation, which seems to be, at least in part, dependent on angiotensin II.

TROPHIC FACTORS: Myocyte and nonmyocyte cell growth can be independent of each other and can be regulated by different factors. The role played by various hemodynamic factors and circulating hormones on the fibrous response of the rat right and left ventricles has been examined in several models of experimental hypertension in the rat. Brilla et al[8] have shown myocytic hypertrophy to be most closely related to ventricular loading, whereas changes in the nonmyocytic compartment seem to be regulated by circulating angiotensin II and aldosterone, either alone or with other humoral factors. This action seems to be fairly specific because aldosterone appears to cause an increase in collagen content without affecting myocytes.

Cardiac fibroblasts may possess corticoid receptors, with which aldosterone may interact to stimulate collagen synthesis. A short-term response may be to augment DNA synthesis in individual cardiac fibroblasts, where increased collagen production predominates over proteolysis by collagenase. A long-term response to mineralocorticoids would seem to be proliferation of fibroblasts. This increase in the number of fibroblasts in turn leads to increased collagen production. This process is thought to be involved in chronic disease states such as arterial hypertension.[4]

Activation of the renin–angiotensin–aldosterone system (RAAS) may lead to abnormal permeability of intramural coronary vessels, which could explain the preferential perivascular localization of myocardial fibrosis in the early stages of its development.

In contrast to other tissues, there is, in general, no evidence that immunologic mechanisms are involved in the structural remodeling process. The interstitium seems to exhibit a degree of autoregulation, although it cannot be stated with any degree of certainty whether this auto-regulation results from the original cardiac disorder or is in fact responsible for accelerating the process of cardiac failure.

HISTOLOGIC FINDINGS IN HUMANS: The data reviewed so far have been from experimental animal models. A number of extremely important findings are available from postmortem studies in humans examining the composition of myocardial collagen in different pathologic states.

Of particular note is the work of Bishop et al,[9] which showed that the concentration of collagen in the left ventricle, based on hydroxyproline content, increased by a factor of 2 in patients with dilated cardiomyopathy and by 30% in patients with coronary artery disease when compared with control subjects. Of the total increase in collagen content, the highest proportion was of type I, the most rigid. It must be borne in mind that these were cadaveric hearts, whereas it is known that type III collagen is produced in the early stages when the disease process is less advanced.

Following myocardial infarction, reparative fibrosis of the necrotic area occurs. Of greater relevance to the subject of cardioreparation are the important structural alterations to the noninfarcted myocardium where the degree of reactive fibrosis has significant prognostic implications.[10]

More recently, it has been demonstrated that ventricular wall stiffness is not always determined by the total amount of collagen present: the architectural organization and in particular the extent of interlinking of fibrillar collagen would appear to be of primary importance in determining ventricular function following aortic valve replacement.

In summary, regardless of the etiology or pattern of development of cardiac failure (Figure 2), interstitial involvement may be a highly important pathologic and dynamic contributory factor. Interstitial changes are 3-fold: quantitative, with an increase in the quantity of collagen and of other glycoproteins; qualitative, with changes in the type of collagen, with a preponderance of the more rigid type I; and finally spatial, through the mechanical alterations that result from structural changes and that lead to functional consequences. It is highly probable indeed that in addition to this there are ultrastructural and molecular changes occurring at the level of the cytoskeleton, although at present these have few obvious clinical implications.

METHODS OF ASSESSMENT

The importance of the myocardial interstitial changes that occur in a number of pathologic states is no longer in doubt. This highlights the potential value of objectively assessing the state of the interstitium at any given time and also to gain insight into the dynamics of the interstitial tissue. Although indirect methods of assessing the myocardial interstitium exist, these are unsatisfactory in that they do not provide a clear picture of the processes taking place. More accurate assessments are required and there are presently 3 possibilities worthy of consideration: (1) direct examination of myocardial biopsy specimens, (2) imaging techniques to evaluate quantitatively myocardial and nonmyocardial components, and (3) measurement of interstitial plasma markers.

Myocardial biopsy: Biochemical and ultramicroscopic methods allow overall measurement and assessment of the type and localization of collagen in animal and human hearts. Collagen quantification in the clinical situation is restricted by the aggressive nature of endomyocardial biopsy, when this is performed, and by the limits imposed by such measurements in a small biopsy fragment. At present, endomyocardial biopsy has only principally been used clinically in Europe to study the myocardial interstitium prior to and following surgery for aortic stenosis.[11]

Although it is possible to gain an approximate impression of whole myocardial collagen content from a small fragment, this method is inherently restricted by differences that may exist between the fragment and the whole organ, such as variability in localization. This problem is found particularly in the early stages of ventricular hypertrophy, where myocardial collagen is most prominent in subendocardial regions. It is mainly for ethical reasons, however, that repeated biopsies in individual patients are not undertaken on a large scale because of the associated risks.

Imaging techniques: echocardiography and magnetic resonance imaging: At present, the functional consequences of myocardial rigidity caused by altered myocardial collagen content or composition are not correlated closely enough with the hemodynamics of ventricular filling to allow these newer measurement modalities to be used as indicators of the degree of fibrosis.

Research with echocardiography has so far confirmed the increased ultrasonic reflectivity of the fibrotic myocardium, and several in vitro and in vivo studies in different pathologic models have shown a good correlation between the amplitude of back-scattered echo and histologically assessed collagen. There are several limitations, however, to the methodologies used that are inherent to both ultrasound and histologic evaluation.[12,13]

Nuclear magnetic resonance imaging (MRI) has the potential for noninvasive tissue characterization of the heart. Fibrosis elsewhere has been recognized by changes in MRI intensity and relaxation times, and both acute and chronic myocardial infarction have also been identified. In vitro MRI studies in animals have investigated the relation between T_1 and T_2 relaxation times, collagen, and water content.[14] In the clinical context, MRI principally allows accurate measurement of regional left ventricular function and mass, magnetic resonance spectroscopy allowing the study of high-energy phosphate metabolism.[15] Currently, however, MRI cannot adequately distinguish between collagen and ventricular muscle, even if the former is present in large amounts.

Further developments are required before ultrasound and MRI tissue characterization can evolve into clinically useful methods to document not only the presence of regional myocardial fibrosis, but also to assess any interventions designed to prevent its appearance or even to cause its regression.

The most realistic methods at present use radioisotope-labeled antibodies in conjunction with positron emission tomography (PET) or single photon emission computerized tomography (SPECT) scans, but it is too early to speculate on the potential clinical applications of these imaging modalities.

Plasma markers: Collagen synthesis and degradation are normally in balanced equilibrium: collagen degradation occurs at a rate of 5% per day and counterbalances collagen synthesis. In other tissues, such as hepatic parenchyma or skeletal muscle, turnover can be assessed by measuring plasma levels of the intact molecule, a part of it, a metabolite, an associated component, or the enzyme system involved. The potential thus exists for using plasma markers to assess collagen turnover, because this involves a balance between synthesis and breakdown (Figure 4).

There are 2 basic problems, however, with the use of plasma markers to assess myocardial interstitial components. When considering the time course of cardiac events, myocardial infarction is the only

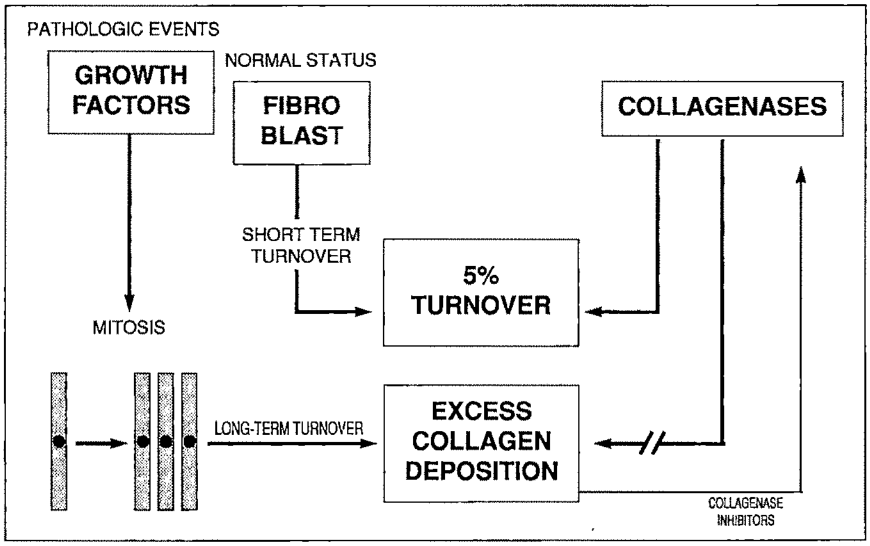

FIGURE 4. Collagen synthesis by fibroblasts and degradation by collagenase are normally in a state of balanced equilibrium. In pathologic situations increased collagen deposition can lead to alterations in the structure of the myocardium.

pathologic state in humans that produces a sudden change in myocardial function that can be compared to the animal experimental model. Clinically, other pathologic states are subacute, or chronic, e.g., hypertension and heart failure. In chronic disease states such as LVH, significant changes in plasma markers are unlikely to occur, making it difficult to apply this method for evaluating interstitial modifications, except in the case of a therapeutic intervention, which might potentially modify plasma marker levels to a significant extent. The second problem relates to the myocardial interstitium itself: despite the development of highly specific protein identification methods, many myocardial constituents are widely distributed within the organism, since they are derived from connective tissue. Any extracardiac pathologic condition may therefore affect concentrations of plasma markers to a much greater extent than the myocardial interstitium itself.

To date, several potential markers can be considered, in particular procollagen III, collagenase, and fibronectin.

PROCOLLAGEN III: Fibroblasts are free to move within the extracellular space and are capable of synthesizing procollagen molecules. Pro-alpha chains are synthesized by translation of the mRNA on the ribosomes, and complex post-translational enzymic modifications occur as the nascent chains pass into the cisterna of the rough endoplasmic reticulum. A triple helix is formed within the smooth endoplasmic reticulum, which is then transported and secreted in Golgi secretory vacuoles.

Conversion of the procollagen molecule to collagen occurs in the extracellular matrix: enzymatic cleavage of the nonhelical propeptides of the procollagen molecule occurs with specific enzymes acting on the N and C terminal regions. This may occur within folds of the fibroblasts or at some distance from the cell, but self-assembly of collagen fibrils occurs immediately following cleavage of the endopeptides, which are then released into the circulation. This self-assembly of collagen molecules into a fiber is followed by their polymerization, providing characteristic strength to the collagen fiber.[16] A 3-dimensional network of covalent intermolecular cross-links is then formed that stabilizes the architectural structure.

The release of the terminal peptides into the circulation during collagen synthesis is of clinical relevance and serum levels of procollagen type III amino-terminal peptide have been measured in humans following myocardial infarction. This peptide was shown to be present as a marker for collagen formation in the myocardium as part of the scarring process for 4 months following infarction, with a release peak occurring between the 3rd and 7th days postmyocardial infarction.[17–19]

Further research to assess the potential use of type III procollagen peptide as a marker for collagen turnover is needed.

COLLAGENASE: The half-life of collagen is 80–120 days. Procollagen is susceptible to intracellular degradation, and in the heart this may account for as much as 60% of total collagen degradation. Once deposited in the interstitium, collagen is a stable protein, and collagen-specific proteolytic digestion is needed to remove it. Collagen fiber breakdown is mediated by collagenase.

Montfort and Perez-Tamayo[20] have identified myocardial collagenase as residing on perimysial fibers between muscle fibers, and also on the endomysial weave that surrounds individual cells. Collagenase is produced by fibroblasts, probably as a procollagenase, which is activated when released into the interstitium. Since fibroblasts do not store it, it seems that collagenase can exist in a latent form, either as a tissue-inhibitor complex or as a zymogen. It is not yet known, however, which of these 2 latent forms exists within the myocardium. Collagenase is specific to collagen protein and it may not be able to distinguish between collagen of various organs or species, although it appears that type III collagen is more susceptible than type I to degradation.[6]

In animal models a 2- to 3-fold increase in plasma collagenase has been demonstrated following experimental myocardial infarction. This increase is paralleled by a decrease in the collagen content of the necrosed areas for 3 hours following coronary artery ligation.[21]

Collagenases, however, do not appear to have been studied in clinical practice.

FIBRONECTINS: The fibronectins are widely distributed glycoproteins that play a key role in the regulation of the interaction between cell and matrix. Plasma fibronectin is synthesized by hepatocytes and can be directly measured in plasma. The level found in plasma depends on activity of the interstitial tissue. Fibronectin may contribute to the 3-dimensional organization of the extracellular matrix and cytoskeleton[22] and can be described as a universal biologic "glue." Particularly high concentrations of fibronectin have been demonstrated on surfaces of cardiac myocytes in perimysial areas, suggesting that fibronectin may play a significant mechanistic role.[23]

Postmortem studies of interstitial tissue from patients with various cardiac pathologic conditions suggest that fibronectin is present when reactive fibrosis occurs and absent from tissue altered by replacement fibrosis.[24] This highlights the role of the complex fibronectin molecule as a link between cardiac myocytes with an important damping function (Figure 5). Further research to assess its role as a potential plasma marker is needed.

THERAPEUTIC PERSPECTIVES

The effect of angiotensin-converting enzyme (ACE) inhibitors on myocardial fibrosis, which has been clearly demonstrated in animals, is one of the most significant contributions to the development of potential therapies for LVH in this decade. In order to understand how ACE inhibitors may be effective, it is necessary to examine the role played by the RAAS in remodeling of the myocardium.

Role of angiotensin II: Recent research has shown that several peptide growth factors influence fibroblast growth and collagen metabolism. There is evidence that angiotensin II may be a predominant trophic factor responsible for promoting interstitial cell growth.

The role played in the development of LVH by nonhemodynamic factors, such as circulating hormones, has been demonstrated in different renovascular and nonrenovascular models of hypertension.[4,8] It appears that changes in nonmyocytic and myocytic compartments can be brought about by different factors: an increase in ventricular load is probably the primary determinant of myocyte growth, whereas the fibrous tissue response is associated with an increase in plasma angiotensin II and/or aldosterone, independent of the hemodynamic state.

Changes found include an increase in the interstitial cell population, in total interstitial collagen, in the thickness of coronary arteriolar walls, and in microscopic areas of myocytic lysis, independent of coronary artery perfusion. Experimental data suggest that angiotensin II is directly responsible for causing microendothelial lesions that increase coronary artery permeability.[4] This abnormal permeability can allow diffusion of growth factors into the myocardial interstitium. Angiotensin II has also been demonstrated to have a cytotoxic effect on cardiac myocytes, causing cellular necrosis and fibrosis in situ and disrupting myocardial integrity. Finally, angiotensin II has been shown in vitro to have a direct mitogenic effect on certain types of fibroblasts.[25]

The part played by angiotensin II in the development of the clinical syndrome of heart failure thus needs to be considered. Angiotensin II can directly or indirectly stimulate fibroblast proliferation, thus playing a role in the increase in interstitial volume. Increased quantities of type I collagen contribute to increased myocardial wall stiffness, which on reaching a critical level causes ventricular filling defects. This deterioration in ventricular filling contributes to the decompensation of the hemodynamic state, leading to a further increase in the activity of the RAAS. Added to these factors, the direct cytotoxic effects already described cause focal necrosis of myocytes, which are replaced by reparative fibrotic tissue. Finally, due to excessive collagen proliferation, myocyte contractility is impaired.

It is thus clear that, whatever the etiology of cardiac failure, myocardial interstitial changes play a role in its development.

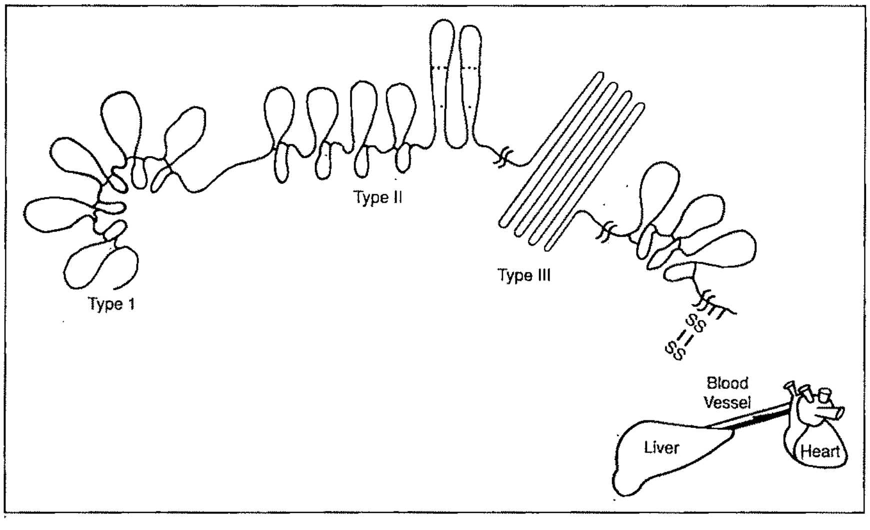

FIGURE 5. Fibronectin is a complex glycoprotein that exists as a cell surface, extracellular matrix, and plasma protein. The fibronectins are thought to have a variety of biologic activities, mostly involving adhesive and ligand-binding functions. Fibronectin is thought to play an important role in the regulation between cell and matrix. It thus appears to be a major component of the myocardial interstitium and may affect myocardial compliance. Fibronectin can be synthesized by a wide variety of cell types. The cell surface form is termed "cellular fibronectin," plasma fibronectin appears to be synthesized by hepatocytes and its levels can be measured directly in human plasma. Further research is needed to assess its potential use as a plasma marker of collagen turnover.

ACE inhibition and animal models of myocardial interstitial fibrosis: There have been a number of reports describing regression of hypertrophy in the myocytic and interstitial compartments of the myocardium and more specifically of collagen content in animal models.

Michel et al[26] showed that the administration of an ACE inhibitor (perindopril) to rats with renovascular arterial hypertension led to a clear reduction in myocyte hypertrophy and collagen content. In spontaneously hypertensive rats (normal renin), however, the ACE inhibitor did not significantly alter myocardial structure. Sen and Tarazi[27] demonstrated balanced regression of myocytic hypertrophy and collagen content with ACE inhibitor treatment, whereas administration of a diuretic or α-methyldopa was associated with regression of myocyte hypertrophy alone, thus leading to a relative increase in the collagen content. Motz and Strauer[28] showed reduction in myocardial hydroxyproline in the spontaneously hypertensive rats treated with a calcium antagonist.

Brilla et al[29] administered lisinopril for 12 weeks (average dose 15 mg/kg/day) to spontaneously hypertensive rats with established LVH and adverse structural remodeling of the cardiac interstitium. Lisinopril reversed fibrous tissue accumulation and medial thickening of intramyocardial coronary arteries and restored myocardial stiffness and coronary vascular reserve to normal. More recently, Brilla et al[30] studied rats with genetic spontaneous hypertension. Two doses of lisinopril (2.5 and 20 mg/kg/day) were administered for 3 months; parameters measured were arterial pressure, left ventricular function, and myocardial collagen content. The lower dose of lisinopril did not reduce blood pressure or cause regression of LVH, whereas the amount of connective tissue was reduced to a level approaching that seen in the control group. Both normalization of blood pressure and regression of fibrosis were observed in the high-dose group. In both cases histologic reparation was accompanied by a decrease in myocardial stiffness toward normal. This reparative process also involved a concomitant decrease in coronary vessel wall thickness.

Clearly, evidence exists to show restoration of myocardial integrity in hypertensive animals. Since we know that in humans an increase in the collagen fraction contributes to the development of heart failure, it is likely that normalizing collagen content will prove to be of benefit in its treatment. Care should be taken, however, when extrapolating data obtained in young experimental animals to that of the clinical condition of heart failure, which is chronic and often has a multifactorial etiology.

Clinical data: In animal models of myocardial infarction, whereas scar tissue is composed of type I collagen, an early increase in type III collagen is seen in the intact myocardium. The role of ventricular adaptation to the loss of viable myocardial tissue has been shown to be important for prognosis in humans in clinical trials with ACE inhibitors. Thus, as ACE inhibitors have been shown in animals to alter the remodeling process beneficially by decreasing the collagen content of myocardium, it could be postulated that the clinical improvement seen in postmyocardial infarction in humans may be the result of a similar process. The results of major clinical trials currently ongoing are eagerly awaited.

Mechanism of action of ACE inhibitors on interstitial myocardial fibrosis: A number of questions remain to be answered on this subject. It is not yet known how ACE inhibitors are able to regress fibrosis. Some or all of the following factors can be considered: (1) a nonspecific action through a reduction in afterload (this effect should also occur with agents from other therapeutic classes); (2) specific and exclusive inhibition of the effects of angiotensin II; (3) a direct action on factors involved in collagen regulation; and (4) inactivation of collagenase inhibitors.

Whatever their mode of action, ACE inhibitors may be used much more extensively in the future for the prevention or treatment of myocardial fibrosis. The need for a reliable method of assessing collagen turnover from a clinical perspective should, therefore, be seriously considered.

CONCLUSION

The concept of cardioreparation implies a restoration of structural abnormalities and a return of cardiac function to or toward normal. Collagen synthesis and degradation are normally in a state of balanced equilibrium. Given our knowledge of the importance of maintaining this equilibrium between the myocytic and nonmyocytic compartments, the time has come to examine the subject of myocardial collagen turnover more closely.

The identification of a plasma marker is of potential clinical significance but is still some way into the future. This issue becomes even more complex when the factors involved in regression of fibrosis, including inhibition of collagen synthesis, regulation of gene expression for collagenases, and finally fibroblast growth factors are considered.

Regardless of questions that remain, the following points must be considered in clinical practice: (1) myocardial interstitial fibrosis appears to be both a response as well as one of the causative or aggravating factors in myocardial failure; and (2) ACE inhibitors appear to have an unprecedented and specific effect on interstitial fibrosis, namely, to prevent, stabilize, and reverse interstitial proliferation.

Much research remains to be undertaken. The molecular mechanisms that initiate the development of myocardial interstitial fibrosis must be identified and reliable clinical methods for assessing the interstitium and the changes that occur within it need to be developed.

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Ventricular Arrhythmias in Heart Failure

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Heart failure is an increasingly common disorder leading to reduced quality and expectancy of life. Asymptomatic and symptomatic ventricular arrhythmias are a frequent complication and have been found to be independent prognostic predictors for sudden cardiac death in patients with heart failure. Unfortunately, the positive predictive value for this finding is low, but in patients with sustained ventricular arrhythmias, variables indicating impaired pump function are the most important predictors of sudden and of nonsudden cardiac death. Arrhythmias in heart failure may have many different underlying mechanisms. Indications for, and mode of treatment of, arrhythmias in heart failure depend on the symptoms and prognostic significance of the arrhythmia. Primarily, pump function should be optimized and antiarrhythmic drug therapy instituted only when the arrhythmia persists. In poorly tolerated and life-threatening arrhythmias, implantable devices allowing pacing and defibrillation must be considered. No data are presently available indicating a protective role of antiarrhythmic drugs in the prevention of sudden cardiac death in heart failure. Future directions should concentrate on the development of better stratification of risk for sudden death, better delineation of mechanisms of arrhythmias in heart failure (allowing the development of mechanism-specific antiarrhythmic drugs), and research into new nonpharmacologic techniques such as cardiomyoplasty and molecular biologic techniques to rebuild the failing heart muscles.

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Ventricular arrhythmias are common in heart failure. Their prevalence has been reported to be 71–95% for couplets and multiform premature ventricular depolarizations and 28–80% for nonsustained ventricular tachycardia.[1]

Ventricular arrhythmias in patients with pump dysfunction show a wide variability in their occurrence and symptomatology. They have also stimulated interest as possible predictors for death, especially sudden death, which in this setting is generally thought to be tachycardic in origin. When and how to treat these arrhythmias is a difficult dilemma.

In clinical practice there are 2 indications for treatment of a disorder: to alleviate symptoms and/or to improve prognosis. In the presence of heart failure, antiarrhythmic drug therapy has been shown to be disappointing for both indications. The negative inotropic effect of many antiarrhythmic drugs restricts their use in heart failure. Proarrhythmic effects may cause the condition of the patient to deteriorate and/or increase the risk for sudden death. In addition, extracardiac side effects may limit the use of sometimes quite effective drugs such as amiodarone.

Therefore, in spite of much effort to improve prognosis in heart failure, it has become clear that there is still a long way to go to achieve this goal.

A more rational approach to the treatment of arrhythmias in heart failure requires answers to a number of questions. The first is to obtain a better knowledge of risk stratification in patients with heart failure: which patients are most at risk for developing life-threatening arrhythmias. The second is to gain better insight into arrhythmogenic mechanisms active in heart failure. It is not unlikely that similar mechanisms may lead both to pump failure and arrhythmogenicity. Understanding that mechanisms other than reentry may play a role in these patients may lead to the development of more specific antiarrhythmic drugs.

RISK STRATIFICATION

Ventricular arrhythmias as indicators of risk for sudden cardiac death in heart failure: Heart failure carries a poor prognosis. Data from the

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Framingham study reveal 1- and 5-year survival rates of 79 and 38% in men and 86 and 57% in women, respectively. Comparable results have been published in more recent studies.[2] The incidence of sudden death varies between these studies but the majority report an occurrence of >40% of total cardiac deaths.[1]

Many clinical and laboratory variables indicating pump dysfunction are related to (sudden) death, such as dyspnea class,[3] the presence of pulmonary congestion,[4] left ventricular ejection fraction,[4] left ventricular size,[5] and exercise time.[6] Other variables indicating the role of the neuroendocrine system include plasma norepinephrine,[6] plasma renin,[6] and biochemical derangements such as hyponatremia and hypokalemia.[6]

Asymptomatic ventricular arrhythmias have been considered as indicators of risk and possible targets for prevention of arrhythmic death.

In ventricular dysfunction after myocardial infarction, arrhythmic death has been found to be related to the number and severity of ventricular ectopic activity.[7–10] This variable was found to be independent of the left ventricular ejection fraction.[7,9,10] Also in other studies of patients with both ischemic heart disease and idiopathic dilated cardiomyopathy as the cause of chronic heart failure, ventricular extrasystoles were found to be related to mortality.[6,8,10]

In several other studies[11–14] no correlation with mortality could be shown. These findings may be partially explained by patient selection. For instance, in the study of Holmes et al[10] 1-year survival was 51%, whereas in the report of Huang et al[11] only 3 of 35 patients suffered cardiac death.

Conflicting data are also reported in a recent analysis of data from the CAST study.[14] Here mortality increased with increasing premature ventricular complex frequency and in patients with >2 episodes of ventricular tachycardia. However, this was only found at baseline in the group randomized to active treatment and could not be confirmed in the placebo group. Because mortality was higher in patients with a higher incidence of preexisting arrhythmias, these findings may be explained by the proarrhythmic properties of the class IC antiarrhythmic drugs. Given the conflicting data, no conclusion can be reached as to the true prognostic relevance of ventricular ectopic activity in heart failure. Even in the studies showing a relation, the absence of ventricular ectopy reliably predicted good prognosis but the positive predictive accuracy was quite low.

Heart failure as an indicator of risk in patients with sustained ventricular tachycardia: The prognosis of a sustained ventricular tachycardia is clearly related to etiology and presence or absence of congestive heart failure. Even with the same etiology, prognosis may differ markedly in relation to pump function.

In a recent analysis[15] of factors related to sudden and nonsudden death in 200 patients with sustained ventricular tachycardia or ventricular fibrillation occurring in the subacute and chronic stage of myocardial infarction, 4 predictive clinical variables were identified. Two of these were expressions of compromised pump function, i.e., dyspnea functional class 3 or 4 and the presence of multiple myocardial infarctions. One other factor was also partially related to pump function, i.e., circulatory arrest at the time of the first spontaneous episode of arrhythmia. The fourth predictor was the early occurrence of sustained ventricular tachycardia or ventricular fibrillation after infarction (3 days to 2 months). Patients with 0 or 1 of these 4 variables had an incidence of sudden death of 2.8% and of 4.2% for nonsudden cardiac death after 2 years follow-up, whereas patients with >2 variables had a 17.5% and 20.3% incidence of sudden and nonsudden death, respectively. The strongest predictor for sudden death was the occurrence of circulatory arrest during the first episode of the arrhythmia and for nonsudden death was the functional class of the patient.

These findings stress the importance of parameters of pump function in assessing the prognosis of patients with sustained ventricular tachycardia.

MECHANISMS OF ARRHYTHMIAS IN HEART FAILURE

Heart failure can be caused by many different disorders, such as hypertension, coronary artery disease (including ischemia and myocardial infarction), valvular heart disease (including insufficient and stenotic valves), dilated and hypertrophic cardiomyopathy, congenital anomalies, brady- and tachyarrhythmias, and asynchronous ventricular contraction due to aberrant conduction or ventricular pacing.

These types of diseases result in different mechanisms of pump dysfunction. These differences are based on such factors as: (1) the type and number of cardiac chambers involved in the disease process; (2) the phase of the cardiac cycle involved (systolic or diastolic); (3) the type and extent of disease in the chamber involved (global or localized, homogeneous or patchy; (4) the load imposed on the chamber: volume or pressure load; and (5) differences in energy supply: increased demand or decreased supply.

As will be discussed below, many of these aspects of pump dysfunction are arrhythmogenic (Table I).

TABLE I Possible Mechanisms of Arrhythmias in Heart Failure

	Reentry	EAD	DAD	AA
Structural				
Scar	+			
Fibrosis	+			
Dilation	+		+	
Hypertrophy			+	
Ischemia	+			+
Neurocontrol				
Sympathetic		+	+	+
Electrolytes				
K+		+	+	
Mg^{2+}		+	+	
Drugs				
Digitalis			+	
Diuretics		+	+	
Vasodilation	+			+
Inotropes	+		+	
Antiarrhythmic agents	+	+		

AA = abnormal automaticity; DAD = delayed after-depolarization; EAD = early after-depolarization.

Mechanisms of arrhythmias are divided into reentry, triggered activity, and abnormal automaticity. Reentry requires 2 different anatomically or functionally divided pathways, with unidirectional block in 1 and slowing of conduction in the other pathway. The latter mechanism can be induced by ischemia and fibrosis, but also by antiarrhythmic drugs such as class IA and IC drugs. Class IC drugs have a rate-related increase of slowing of conduction, which may result in initiation of reentrant tachycardias on reaching a critical heart rate (Figure 1).[16]

TRIGGERED ACTIVITY: Two types of triggered activity leading to ectopic spontaneous activity can be recognized: those based on early or on delayed after-depolarizations.[17] Early after-depolarizations probably play an important role in ventricular arrhythmias in the long QT syndrome (torsade de pointes). Occurrence of early after-depolarizations is promoted by electrolyte disturbances such as hypokalemia and hypomagnesemia, and some class IA and class III drugs are able to induce proarrhythmic effects based on early after-depolarizations in some patients.

Triggered activity, based on delayed after-depolarizations, was first recognized as the underlying mechanism of digitalis-induced arrhythmias in isolated tissue and later in digitalis-induced ventricular tachycardia in the intact heart.[18] Also, elevated circulating catecholamines and other pathophysiologic conditions such as electrolyte disturbances, ventricular hypertrophy, and damaged myocardial tissue,[19] have been found to promote induction of delayed after-depolarizations. In addition, stretch of Purkinje fibers (as in ventricular dilation, increased wall stress, or diastolic pressure elevation) has been found to increase the amplitude of delayed after-depolarizations.[20]

The common denominator in these pathophysiologic circumstances is intracellular calcium overload. This mechanism is thought to play a central role in heart failure, because in this condition the cardiac myocytes are not able to maintain a low cytoplasmic calcium level.[21] Increased cytoplasmic calcium induces calcium release from the sarcoplasmic reticulum and subsequent sodium–calcium exchange through the sarcolemmal membrane. The latter results in triggered activity and delayed after-depolarizations.[22]

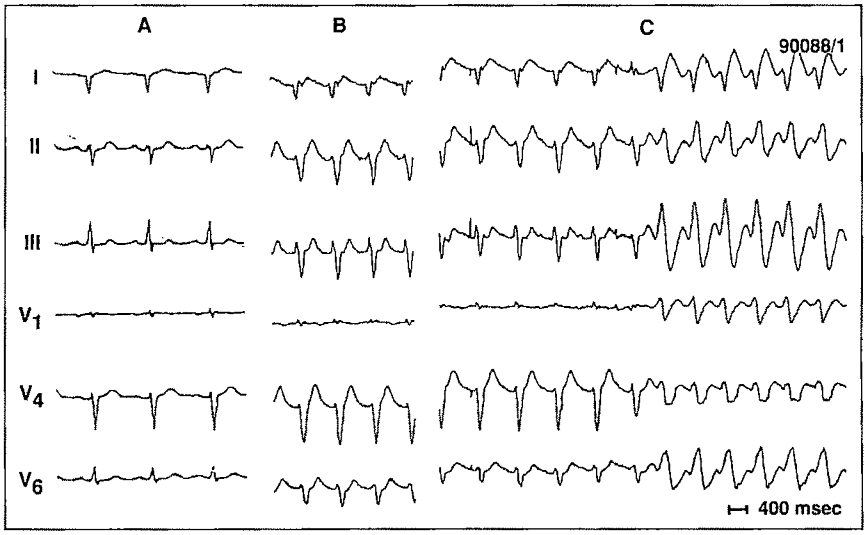

FIGURE 1. Class IC drug-induced slowing of conduction during exercise leading to ventricular tachycardia. *A*, electrocardiogram recorded before exercise. *B*, widening of the QRS complex during exercise-induced sinus tachycardia. *C*, widening of the QRS complex during sinus tachycardia is followed by ventricular tachycardia.

Apart from delayed after-depolarizations, intracellular calcium overload leads to electrical uncoupling[23] and subsequent electrical heterogeneity, which may act as possible mechanisms of ventricular tachycardia.[21] Our group has demonstrated that calcium overload blockers such as flunarizine selectively suppress triggered activity (Figure 2).[24,25]

Because many of the conditions mentioned are present in the intact failing heart, it is likely that in those patients, triggered activity is an important mechanism of clinical arrhythmias.

ABNORMAL AUTOMATICITY: Abnormal automaticity is spontaneous impulse formation arising from a reduced diastolic membrane potential.[26] It occurs as a mechanism for ventricular tachycardia in the 24-hour myocardial infarction model in the canine heart. It may also play a role in myocardial ischemia because under these circumstances reduction of diastolic membrane potential is present.[27]

These considerations indicate that arrhythmias in heart failure may be based on different arrhythmogenic mechanisms alone or in combination. Scar tissue and fibrosis provide the anatomic substrate for delayed impulse reentry,[28] whereas ischemia may promote premature reentry by inducing conduction.[29] Ventricular dilation and hypertrophy may lead to delayed after-depolarizations and triggered activity.[20,30,31] Dilation may also result in conduction block,[32] abbreviation of the ventricular effective refractory period, dispersion of refractoriness, and an increase in epicardial and endocardial differences in duration of the refractory period.[33] Those changes also favor the development of reentry arrhythmias.

In humans, the presence of left ventricular hypertrophy has been found to be arrhythmogenic.[34] Increased sympathetic tone may induce or accelerate occurrence of early after-depolarizations,[35] delayed after-depolarizations,[36] and abnormal automaticity.[37]

TREATMENT OF ARRHYTHMIAS AND PREVENTION OF ARRHYTHMIC DEATH

One of the most difficult dilemmas for the clinical cardiologist is when and how to treat arrhythmias in patients with heart failure. Arrhythmias occur in a complicated setting of electrical instability, ischemia, and/or pump failure (Figure 3). Therefore, ischemia and pump failure should be optimized before prescription of antiarrhythmic agents, because their negative inotropic properties and proarrhythmic effects may be hazardous. Figure 3 also shows that many of the factors influencing blood supply, pump function, and electrical behavior are dynamic and not static. For example, in ischemia, spasm or intimal rupture of a coronary artery leading to thrombosis may suddenly change the static situation of a fixed atherosclerotic narrowing. This indicates the necessity of individualization of treatment. Pump function must be optimized, ischemia must be corrected, and modulating factors must be controlled, for instance by β-blockade[38] and/or angiotensin-converting enzyme (ACE) inhibition.

Inotropic drugs that reduce, or at least do not increase, heart rate are important in this respect. From this point of view, digitalis is an interesting

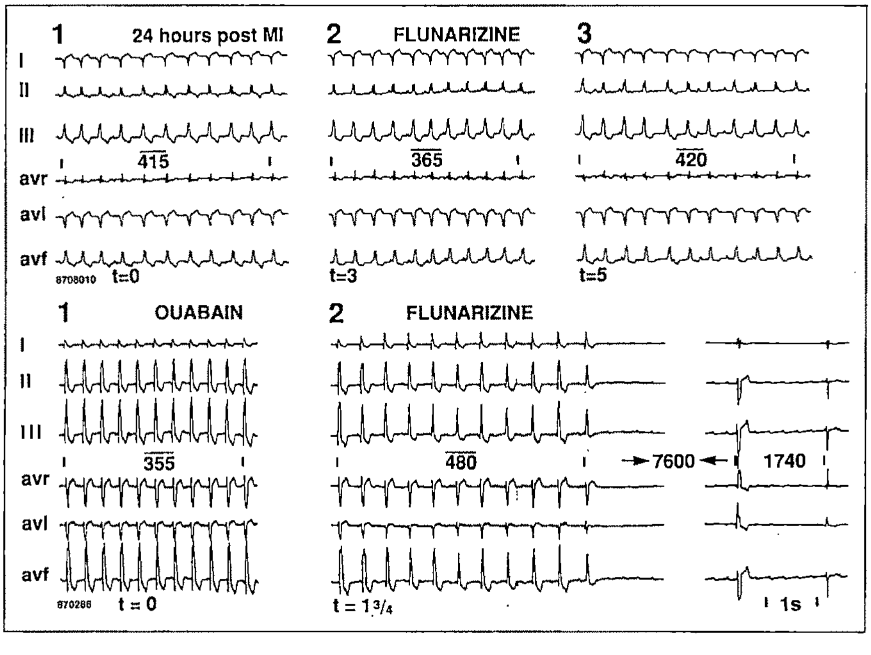

FIGURE 2. Illustration of the specific effect of flunarizine on delayed after-depolarization–related triggered activity. *Lower panel:* termination of digitalis-induced arrhythmia by flunarizine. *Upper panel:* absence of effect of flunarizine on ventricular tachycardia 24 hours after myocardial infarction (abnormal automaticity).

drug because it improves contractility without increasing heart rate.

The decision to use antiarrhythmic therapy in heart failure, therefore, depends on the answers to the following questions: Is the arrhythmia already controlled by correcting ischemia and optimizing pump function? If no, does the arrhythmia produce symptoms, and is the arrhythmia of prognostic significance (increased risk of arrhythmic death)?

If the arrhythmia is controlled by improving pump function and by controlling ischemia and the modulating factors, there is no obvious reason to institute antiarrhythmic drug treatment. Many arrhythmias, however, persist after these steps have been taken. An example is sustained ventricular tachycardia in the setting of an old myocardial infarction. Although ischemia may be present, coronary revascularization is insufficient to cure or prevent the arrhythmia and additional measures to control or remove the substrate are indicated. In case the arrhythmia produces symptoms, some form of antiarrhythmic treatment must be instituted.

If the arrhythmia does not lead to circulatory arrest, antiarrhythmic drugs are usually sufficient. Drug selection may be helped by the evaluation of the effectiveness of the drug by programmed electrical stimulation,[39,40] especially in the case of sustained forms of ventricular tachycardia, although the possible proarrhythmic and negative inotropic effects of antiarrhythmic drugs must be considered. Also, extracardiac side effects may limit the use of these drugs. In this regard, class IA drugs are less frequently indicated than other drugs with less negative inotropic effects.

Evaluation of proarrhythmic effects: Class IA and class III antiarrhythmic drugs tend to induce QT prolongation and torsade de pointes. In the case of class IA drugs, this complication frequently occurs within the first days of treatment, facilitating early recognition during clinical observation. A possible indicator of an increased tendency to develop this proarrhythmic complication is the opposite behavior of the QT_c interval during exercise. Recent data suggest that during the recovery phase after exercise, the QT_c interval tends to be prolonged in untreated patients prone to develop torsade de pointes.[41] The predictive value of this finding awaits further evaluation. Class IC drugs have a rate-related increase of slowing of conduction, which may lead to the induction of reentrant tachycardias.[17] Therefore, exercise testing during class IC administration is mandatory to evaluate possible proarrhythmic effects of these drugs.

Further control of proarrhythmic effects may be achieved by careful follow-up of kidney and liver function and plasma potassium and magnesium levels. In the cases of low drug efficacy using class IA, IC, or class III drugs, or other reasons for termination of the antiarrhythmic drug, the use of amiodarone[41] should be considered. This drug has a high efficacy, good initial tolerance, minor negative inotropic and proarrhythmic effects, and easy dosing schedule. The high incidence of long-term side effects restricts widespread use and high dosing, although most side effects are reversible.

Arrhythmias leading to circulatory arrest: In arrhythmias leading to circulatory arrest, a more aggressive diagnostic and therapeutic approach must be followed. Programmed stimulation can be useful in initiating the clinical arrhythmia.[39,40] If the tachycardia is hemodynamically tolerated, mapping of early local electrical activation may indicate the origin of the tachycardia.

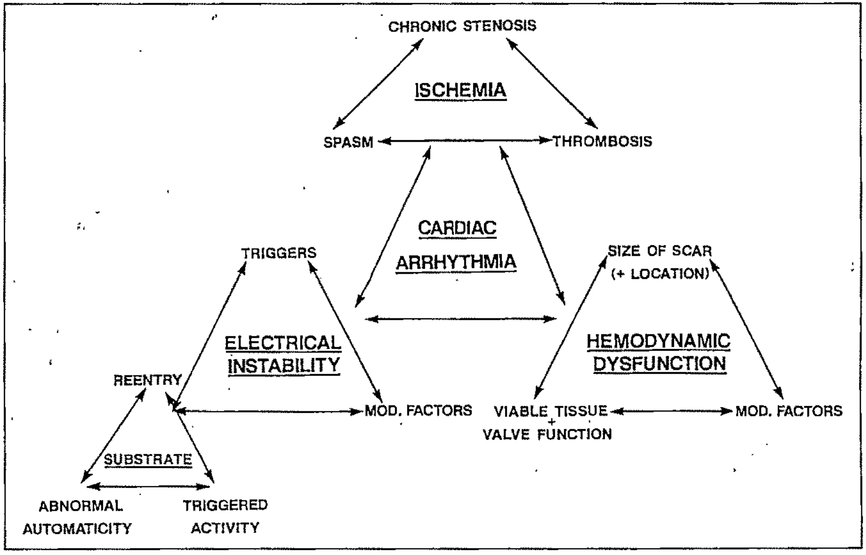

FIGURE 3. Model showing the interplay between different pathophysiologic mechanisms in the induction of arrhythmia. All mechanisms have static and dynamic components. Modulating (MOD.) factors include the autonomic nervous system, electrolytes, hormones (renin–angiotensin system), and drugs.

Accurate localization facilitates surgical or catheter destruction or isolation of the tissue from which the tachycardia originates. Subendocardial resection, endocardial circumcision, and aneurysmectomy combined with cryoablation are surgical options. Chemical, electrical, and radiofrequency ablation are catheter methods to ablate ventricular arrhythmogenic cardiac tissue.

In tachycardias that are not hemodynamically tolerated, localizing the origin of tachycardia is difficult or impossible. Therefore, surgical treatment cannot be map-directed and implantation of internal antitachycardia devices will frequently be necessary.

If no nonpharmacologic approach is possible, treatment with amiodarone is indicated, which may be combined with other drugs from class I or III.[42,43]

Asymptomatic arrhythmias indicating poor prognosis: As has been pointed out before, ventricular premature beats (especially when complex) and frequent and nonsustained ventricular tachycardias have been considered possible indicators of poor prognosis in patients after myocardial infarction and heart failure. Our current experience indicates that there are different reasons not to attempt to suppress these arrhythmias. Their predictive value is low, which means that overtreatment occurs in the patient group presenting with these arrhythmias. Also because of proarrhythmic effects, the induction of new or aggravation of existing arrhythmias is a potential risk.

Prevention of sudden death in heart failure: Several studies[44–46] such as Studies of Left Ventricular Dysfunction, (SOLVD), Vasodilator–Heart Failure Trial (V-HEFT), and the first Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS I) have demonstrated that cardiac death rate can be diminished by treatment of moderate[44] and severe[46] heart failure. This has been shown for ACE inhibitors[44,46] and isosorbide dinitrate plus hydralazine.[45]

Although initial studies did not show a reduction in sudden cardiac death, recent data comparing enalapril with hydralazine–nitrate[47] suggest a reduction in sudden rather than nonsudden death. This finding may be explained by ACE inhibitor-induced reduction of neurohumoral stimulation.

Increased mortality rates have been reported during prolonged use of β-adrenergic agonists such as xamoterol[48] and phosphodiesterase inhibitors such as milrinone in patients with severe heart failure.[49]

Limited experience is available in relation to antiarrhythmic drug treatment and prevention of sudden cardiac death in heart failure.[50]

Studies are currently in progress, for example with amiodarone, on the effectiveness of antiarrhythmic drug therapy in relation to survival in heart failure.

FUTURE DIRECTIONS

There is a need for better stratification of patients with heart failure at risk of sudden death. There is a lack of a single noninvasive risk parameter with a sufficiently high positive predictive accuracy. Accurate identification of high-risk patients allows the evaluation of more aggressive pharmacologic and nonpharmacologic treatment, such as electrical devices with pacing and defibrillation capabilities.

Early recognition and treatment of disease states leading to heart failure, such as ischemia, myocardial infarction, and hypertension, should be attempted.

Further developments are required in relation to recognition and treatment of mechanisms of arrhythmias in heart failure. In particular, the relevance of delayed after-depolarization–induced triggered activity should be evaluated, since this may lead to more specific drugs and a lower incidence of proarrhythmia, negative inotropy, and extracardiac side effects. Future trials should be based on better information on the mechanisms underlying arrhythmias in heart failure: although presently most attention is given to pure class III antiarrhythmic drugs, it should be realized that these drugs are effective only in reentrant arrhythmias. The role of the latter in heart failure has not been clarified.

Finally, approaches to improve cardiac contractility have to be awaited, such as cardiomyoplasty, new pharmacologic interventions, and molecular biology techniques, which allow the heart muscle to be restored.

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Electrolyte Balance in Heart Failure and the Role for Magnesium Ions

Per Olof Wester, MD

It is well established that clinically significant changes in a number of electrolytes occur in patients with congestive heart failure (CHF). Magnesium ions are an essential requirement for many enzyme systems, and evidence is rapidly emerging that magnesium deficiency is a major risk factor for survival of CHF patients. In animal experiments, magnesium has been shown to be involved in several steps of the atherosclerotic process and, although in humans the situation is somewhat more complex, magnesium ions play an extremely important role in CHF and various cardiac arrhythmias. A number of drugs commonly used to treat CHF can significantly affect not only cellular magnesium ion homeostasis, but potassium as well. These include mercurial, thiazide, and loop diuretics. It has also been reported that hypomagnesemia is common in digitalis intoxication. In contrast, a number of agents have been shown to have either a magnesium-conserving effect (potassium-sparing diuretics) or not to affect magnesium ion balance (angiotensin-converting enzyme inhibitors). The clinical consequences of magnesium deficiency include the development of various cardiac arrhythmias, all of which respond well to magnesium treatment. Thus, it is more than apparent that magnesium ion homeostasis is of major importance in CHF. Future studies should address the complex role of magnesium ions in electrolyte imbalance, particularly in relation to heart failure.

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It has been established that our most abundant intracellular cation, potassium, is necessary for the functioning of the heart. There is now increasing evidence from both experimental and clinical data that our second most abundant intracellular cation, magnesium, is also of great importance in various fields of cardiology, including congestive heart failure (CHF).

The magnesium ion has played an important role in the biologic evolution toward more advanced and differentiated organisms with a more effective use of energy. About 3 billion years ago, chlorophyll was formed, which is the basis for energy production from sunlight, water, and carbon dioxide. Magnesium is an essential part of the chlorophyll molecule. About 2 billion years ago, oxidative phosphorylation evolved, for which magnesium is indispensable. It also has a critical role in the activation of energy storage and utilization. The fact that magnesium is necessary for the metabolism of adenosine triphosphate (ATP) means that it is essential in basic physiologic energy-demanding processes such as muscle contraction (heart muscle included), neuromuscular excitability, cell membrane permeability, and mitochondrial function. Thus, magnesium may be called our "energy ion," and overall it is a necessary requirement for more than 300 enzyme systems, including many in the cardiovascular system.

MAGNESIUM AND CARDIOVASCULAR DISEASE

In animal experiments, magnesium deficiency has been shown to be involved in several steps of the atherosclerotic process, including the metabolism of elastin, collagen, and lipids, as well as platelet aggregation.[1] Under the microscope, experimental magnesium deficiency is manifested by swelling and vacuolization of the mitochondria and distortion of the mitochondrial cristae, and also by infiltration of mononuclear cells, edema, calcification, focal necrosis, and fibrosis.[2] Magnesium deficiency in animals can also give rise to vasoconstriction (coronary, pulmonary, peripheral), which may lead to hypertension.

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In humans the situation is more complex. The magnesium ion has been proposed to be of importance in CHF and for various forms of cardiac arrhythmias. Magnesium may also be beneficial in the treatment of acute myocardial infarction[3,4] and in arterial hypertension.[5]

MAGNESIUM IN CONGESTIVE HEART FAILURE

Electrolyte disturbances are common in treated CHF patients.[6] Potassium, magnesium, and sodium concentrations in plasma and skeletal muscle have been studied in 297 patients with CHF and/or hypertension treated with diuretics, of whom 239 were also receiving digitalis therapy. The incidence of hypokalemia (<3.6 mmol/liter), hypomagnesemia (<0.80 mmol/liter), and hyponatremia (<134 mmol/liter) was 42, 37, and 12%, respectively. Intracellular electrolyte changes, calculated from skeletal muscle biopsies, were even more frequent. Muscle potassium depletion (<40.7 mmol/100 g fat-free dry solids) was observed in 57% and muscle magnesium depletion (<4.03 mmol/100 g fat-free dry solids) in 43% of patients. An increase in muscle sodium (>21.3 mmol/100 g fat-free dry solids) was found in 57% of patients.[6] A still higher frequency (66%) of low muscle magnesium in treated CHF has been reported in patients with chagasic cardiomyopathy.[7] Intracellular potassium and magnesium are also reported to be low in untreated patients with CHF,[8,9] although the prevalence of low serum magnesium in mild CHF may not be very prevalent and may also be uncorrelated to tissue magnesium levels.[10]

There are many factors influencing electrolytes in CHF patients, such as a low daily intake and reduced absorption, renal hypoperfusion, various hormonal compensatory mechanisms, and also treatment. Among operating hormonal compensatory mechanisms, vasopressin and atrial natriuretic factor act mainly on sodium and water balance, whereas the renin–angiotensin aldosterone system (RAAS) and the catecholaminergic system have an influence on potassium and magnesium metabolism.

A low cardiac output and redistribution of blood flow leads to a diminished kidney blood supply and activation of the RAAS. Aldosterone directly stimulates distal tubular cell resorption of sodium in exchange for potassium and hydrogen ions, the net effect being sodium retention, hypokalemia, and alkalosis. Aldosterone has no direct effect on magnesium; however, the increased extracellular volume in CHF leads to a decrease in the proximal tubular resorption of magnesium.[11,12] Sodium resorption is also inhibited in the proximal tubuli; however, in the distal part, sodium resorption is increased but magnesium absorption remains unaffected, resulting in decreased urinary excretion of sodium and increased excretion of magnesium and potassium.

Changes in electrolytes may, in turn, have effects on the RAAS. Low plasma levels of several ions, such as chloride,[13] potassium,[14] magnesium,[15,16] and sodium,[14] stimulate renin release. There is also a counterregulation. Very low plasma potassium levels decrease aldosterone secretion, and severe hypokalemia inhibits aldosterone secretion more than it stimulates renin secretion.[14] However, the action on magnesium seems not to be counterregulated, which may lead to a further magnesium loss.

Catecholamines have complex effects on electrolytes (Figure 1). Epinephrine and norepinephrine stimulate renin release via a β_1 agonist action.[14,17] The resulting raised aldosterone concentration will lead to lowered extra- and intracellular potassium and magnesium levels. Epinephrine stimulates sodium, potassium adenosine triphosphatase (Na^+, K^+-ATPase) in skeletal muscle via a β_2-agonist action, which will lead to reduced plasma potassium but increased intracellular potassium.[18] Epinephrine elevates plasma glucose and insulin release, which leads to decreased plasma potassium and increased intracellular potassium.

Infusions of epinephrine (β_1- and β_2-agonist action)[19,20] and of albuterol (β_2-agonist action)[20] have been shown to reduce plasma magnesium levels in humans. In a study on sheep it has been found that the hypomagnesemic effect of epinephrine is nullified by nonselective β blockade,[21] and it

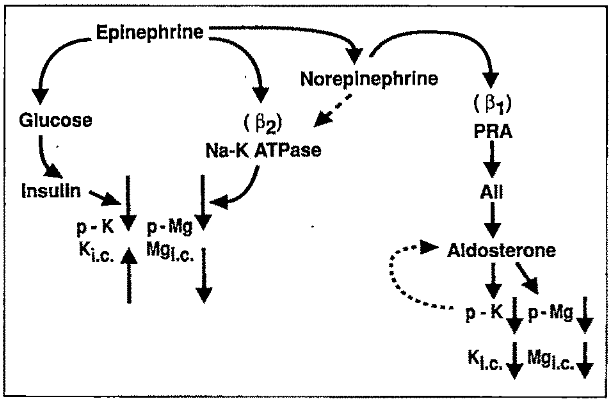

FIGURE 1. Schematic representation of the role of catecholamines in electrolyte homeostasis. AII = angiotensin II; β_1 = β_1-adrenergic stimulation; β_2 = β_2-adrenergic stimulation; i.c. = intracellular; K = potassium; Mg = magnesium; Na-K ATPase = sodium-potassium adenosine triphosphatase; p = plasma; PRA = plasma renin activity.

has been suggested that the effect on plasma magnesium levels is a result of β_2-adrenergic stimulation.[20] The effect may be mediated by stimulation of lipolysis and increased magnesium uptake by adipocytes.[22,23] Epinephrine infusions have been found to deplete magnesium in rats' hearts, possibly as a result of the inhibition of magnesium transport through a postulated magnesium-specific intermediate channel.[24]

TREATMENT WITH DIURETICS AND DIGITALIS

Apart from the deteriorating effects on potassium and magnesium homeostasis induced by hormonal regulatory mechanisms in CHF, some drug treatments may worsen the electrolyte balance.

DIURETICS: Treatment with diuretics is still a cornerstone in the management of CHF, since the intense resorption of salt and water is one of the main problems causing the majority of symptoms. Diuretics are very efficient in moving the ventricular function curve to the left, relieving congestive symptoms. However, with regard to electrolyte homeostasis, the long-term use of diuretics brings with it several problems. Continued use of these agents may lower blood volume, leading to a shift down the ascending part of the curve. The decreased cardiac output will stimulate the RAAS, counteracting the diuretic effect and also leading to loss of extra- and intracellular potassium and magnesium. Further, diuretics may elicit a pronounced effect on the renal handling not only of sodium and potassium, but also of magnesium. Although very little attention has focused on diuretic-induced renal losses of magnesium, except during the last few years, it has been amply demonstrated, since the late 1950s, that significant magnesium losses occur following diuretic treatment.[25] This effect has been observed with mercurial, thiazide, and loop diuretics.[26,27]

The amount of magnesium loss depends on the type of diuretic, the dose, the dosage interval, the length of treatment, and not least the underlying disease. Different types of diuretics exert their renal effects on different parts of the nephron.

The loop diuretics furosemide and ethacrynic acid exert their main action in the ascending part of the loop of Henle, where most (65%) of the filtered magnesium is resorbed. Thus, it is not surprising that these agents are especially liable to produce magnesium deficiency. However, even the thiazide diuretics give rise to magnesium deficiency following long-term administration, despite the fact that these agents are active in a segment of the nephron where only 2–5% of the filtered magnesium is resorbed. Contributing to the magnesium losses may be other factors induced by the thiazide treatment, such as changes in extracellular volume, secondary aldosteronism, interaction with calcium metabolism, or an increased sodium load. Thiazides with a longer biologic half-life tend to produce greater losses of magnesium, as do shorter dosage intervals.

DIGITALIS: Treatment with digitalis may also elicit electrolyte changes. Digitalis is a known inhibitor of Na^+,K^+-ATPase, which gives the energy to the sodium–potassium pump. Magnesium is essential for Na^+,K^+-ATPase function. Thus, digitalis therapy, like magnesium deficiency, will impair the function of the sodium–potassium pump, leading to increased intracellular sodium and decreased intracellular potassium. Further, digitalis treatment causes increased loss of magnesium by reducing the tubular resorption,[28] which may lead to magnesium deficiency. Magnesium deficiency may lead to potassium deficiency and potassium deficiency completes the vicious cycle by reducing the tubular secretion of digitalis.[29] It has been reported that hypomagnesemia is common in digitalis intoxication.[30]

ELECTROLYTE DERANGEMENT: Thus, there are several factors contributing to the derangement of electrolytes in patients with CHF. A low dietary intake and reduced absorption may contribute. Hormonal compensatory mechanisms lead to intracellular potassium and magnesium depletion and sodium accumulation. Digitalis treatment influences the electrolytes in the same direction through impaired function of the sodium–potassium pump and also by increased urinary magnesium wasting. Diuretic therapy causes potassium and magnesium losses. Magnesium deficiency also impairs the proper function of the sodium–potassium pump. Further, intracellular magnesium is considered to be an inward potassium rectifier, which supports the view that internal magnesium functions as a potassium channel-blocking agent, preventing outward movement of potassium ions.[30]

Because potassium is the key ion for the membrane potential, it has long been thought proper to try to replace the potassium losses by potassium supplementation. However, it has been demonstrated in both experimental and clinical studies that low intracellular potassium cannot be corrected with potassium substitution when there is a concomitant magnesium deficiency, as is often the case in patients with CHF. The reason for this might be that magnesium is a necessary cofactor for Na^+,K^+-ATPase. Thus, in magnesium deficiency the pump function for moving potassium into the cell and sodium out of the cell is impaired. Further, an increase in plasma potassium levels induced by potassium substitution will lead to increased aldosterone secretion, leading to further potassium and magnesium losses.

In an investigation involving 79 initially hypokalemic patients on long-term diuretic treatment for arterial hypertension and/or CHF, we studied skeletal muscle electrolytes before and after correction of the hypokalemia.[31] The biopsies on admission revealed that most patients had low muscle magnesium levels, and correction of the hypokalemia did not increase the skeletal muscle potassium levels. On the contrary, a small decrease was observed, probably reflecting an increased aldosterone secretion in response to the increase in serum potassium levels. In contrast, a small group of hypokalemic patients with a normal muscle magnesium content and an isolated potassium deficiency showed a significant increase in skeletal muscle potassium following correction of the hypokalemia.[31] An extension of this study demonstrated that potassium infusions to patients on long-term diuretic treatment did not increase the intracellular potassium content, despite a significant increase in serum levels, nor was there any change in the occurrence of ventricular ectopic beats. When these patients were given a magnesium infusion, their intracellular potassium content increased significantly, and simultaneously the frequency of ventricular beats was significantly reduced.

It is possible to use drugs and/or dietary supplements to avoid the electrolyte disturbances observed in CHF patients. Several groups[32–35] have shown that the potassium-sparing diuretics amiloride, spironolactone, and triamterene also have a magnesium-conserving effect. It has also been shown that the addition of magnesium supplementation to CHF patients already receiving potassium supplementation leads to improvement of their intracellular potassium and magnesium deficit.[36] Infusion of magnesium to severely electrolyte-depleted CHF patients also reduced their intracellular sodium excess.[37] The use of angiotensin-converting enzyme (ACE) inhibitors may also avoid electrolyte disturbances. ACE inhibitors are well known to increase serum potassium levels and to attenuate thiazide diuretic-induced urinary potassium losses.[38] Serum magnesium levels seem not to be affected,[39–41] or are possibly raised.[42] ACE inhibitors have been found to increase[43] or decrease[41] urinary magnesium excretion. Studies on the effect of ACE inhibition on intracellular electrolytes are relatively sparse. No major effects on muscle potassium and magnesium were found in a small study comparing β blockade and ACE inhibition in hypertensive patients.[40]

TABLE I Magnesium-Sensitive Arrhythmias

Ventricular tachycardia	
Ventricular fibrillation	With or without hypomagnesemia
Torsade de pointes	
Digitalis-induced arrhythmias	
Paroxysmal atrial tachycardia	With hypomagnesemia
Atrial flutter and fibrillation	
Multifocal atrial tachycardia	With or without hypomagnesemia

MAGNESIUM AND ARRHYTHMIAS

There is substantial evidence from a large number of case reports published since 1935 that magnesium deficiency may be reasonably assumed to be a factor in the development of various tachyarrhythmias.[43–45] Much of the evidence is provided by the resistance to conventional therapy and the positive response to magnesium treatment. These features may occur in both hypomagnesemic and normomagnesemic patients, possibly because serum magnesium is not always a good indicator of magnesium deficiency.

Table I summarizes various kinds of arrhythmias influenced by magnesium. Torsade de pointes is a form of ventricular tachycardia characterized by widened QRS complexes fluctuating around an isolectric baseline and with varying RR intervals, which are nearly always associated with a prolonged QT segment. This arrhythmia has been repeatedly reported in many case histories to reconvert to sinus rhythm following magnesium infusions.[45] Supraventricular tachycardias have only occasionally been found to respond well to magnesium infusions.

Some serious arrhythmias occurring after acute myocardial infarction may be prevented by magnesium therapy.[3] A large number and wide variety of arrhythmias are induced by digitalis and during diuretic treatment in CHF, some of which may have a common underlying mechanism that is influenced by the magnesium ion. The importance of disturbances in potassium metabolism in clinical cardiology is well recognized, and the risk of arrhythmias in patients with hypokalemia, especially in connection with digitalis therapy, is familiar. Changes in the resting membrane potential caused by an altered relation between extra- and intracellular potassium are thought to underlie the increased ventricular irritability. Disturbances in the relative potassium concentrations in the extra-

TABLE II Electrophysiologic Effects of Magnesium

Magnesium Excess	Magnesium Deficiency
Sinus node—decreased heart rate	Sinus node—increased heart rate
Reduction of intraatrial and atrioventricular (AV) conductance (AV block)	
Extension of the absolute refractory period	Shortening of the absolute refractory period
Shortening of the relative refractory period	Extension of the relative refractory period

and intracellular spaces may lead to changes in potassium conductance across the cell membrane and the repolarization of the cell, resulting in an increased risk of developing reentry arrhythmias. The magnesium ion may influence the incidence of cardiac arrhythmias in different ways. One principal mechanism is through an effect on potassium metabolism. Other possibilities include a direct electrophysiologic effect, or through an effect on calcium metabolism. The electrophysiologic effects of magnesium are shown in Table II.

Excess magnesium retards the periodicity of the sinus node and reduces intraatrial and intraventricular conduction, which may lead to varying degrees of atrioventricular block. There is an extension of the absolute, and a shortening of the relative, refractory periods with magnesium. In magnesium deficiency, the situation is reversed, with shortening of the absolute and extension of the relative refractory periods, which means that the duration of the vulnerable period is increased, resulting in a greater risk of arrhythmias.[46]

The magnesium ion also has a close correlation to calcium metabolism. Magnesium is necessary for the release of parathormone and also for the action of parathormone on bone, kidney, and gut.[47] In addition, magnesium is considered to be a natural calcium antagonist,[48] affecting uptake, content, binding, and distribution of calcium in smooth muscle cells.[49] Further, in magnesium deficiency there is a decrease in intracellular potassium and an increase in intracellular sodium. The increased sodium stimulates the sodium/calcium countertransport: 3 mol Na^+ are exchanged for 1 mol Ca^{2+}. The result will be increased intracellular calcium, which may give rise to oscillatory after-potentials, and arrhythmias.

CONCLUSION

Electrolyte changes, both extra- and intracellular, are very common in patients with CHF, especially those treated with digitalis and diuretics of the thiazide or loop type. As to whether these commonly occurring disturbances in potassium and magnesium metabolism are of significance in relation to the very high frequency of arrhythmias and sudden death that occurs in CHF patients is a matter for debate.

Potassium is responsible for the membrane potential, and changes in either extra- or intracellular potassium may give rise to arrhythmias. Magnesium is of importance for this relation between extra- and intracellular potassium. Further, a low magnesium level may be arrhythmogenic, by allowing more calcium to enter the cell, as well as being arrhythmogenic in itself. Changes in serum potassium concentrations are just one of several prognostic factors for survival in CHF.[50] Recently, a low serum magnesium level has also been found to be related to increased occurrence of ventricular arrhythmias and a significantly reduced 1-year survival of CHF patients.[51]

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Effect of Angiotensin-Converting Enzyme Inhibitors on the Peripheral Circulation in Heart Failure

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In patients with chronic heart failure, the increase in blood flow to working muscle is attenuated and oxygen consumption is lower for any given workload of exercise, compared with normal subjects. This impaired metabolic vasodilation during exercise cannot be restored with short-term administration of angiotensin-converting enzyme (ACE) inhibitors. However, long-term ACE inhibition increases blood flow to skeletal muscle, and this increase is closely correlated with improvement in systemic oxygen consumption. The delayed effect of ACE inhibitors may be related to an interference with the vascular tissue renin–angiotensin system and remodeling of the vascular wall. In addition, endothelial-dependent dilation in response to acetylcholine is blunted in the forearm of patients with chronic heart failure, indicating an impaired endothelial function in this setting. There is experimental evidence that long-term ACE inhibition improves endothelial dysfunction; thus, one might speculate that the beneficial long-term effect of ACE inhibitors on peripheral flow may be, in part, related to its ability to restore normal endothelial function. Vasodilators such as hydralazine that improve blood flow to working muscle after acute administration do not increase skeletal muscle oxygen consumption, indicating that oxygen utilization is not improved. Ultrastructural analysis of skeletal muscle revealed that intrinsic alterations of skeletal muscle exist in patients with chronic heart failure; that is, the oxidative capacity of skeletal muscle is impaired in severe heart failure and contributes to the reduced exercise capacity. Evaluation of skeletal muscle biopsies before and after long-term ACE inhibition revealed that the oxidative capacity of skeletal muscle can be increased after long-term therapy, thereby partially reversing the intrinsic alterations of working muscle in patients with chronic heart failure. It is concluded that the beneficial effect of ACE inhibitors is related, in part, to peripheral mechanisms (i.e., the ability of the peripheral vessels to dilate) and by improving peripheral oxygen utilization.

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It is now well established that the degree of ventricular dysfunction in congestive heart failure (CHF) does not correlate with the severity of clinical CHF, that is, the functional status of patients with CHF as assessed by exercise testing appears to be unrelated to indexes of left ventricular dysfunction.[1] An important factor determining exercise performance in patients with chronic heart failure appears to be an impaired perfusion of skeletal muscle during exercise. Also, almost 20 years ago, Zelis et al[2] first noted that in patients with chronic heart failure, the increase in blood flow to working muscle with exercise is attenuated for each given work load compared with that in normal persons, and this observation was confirmed more recently for large muscle mass by Sullivan et al.[3] Oxygen consumption at each level of work was lower in patients with chronic heart failure and was accompanied by an early increase in plasma lactate concentration.[2] The reduced maximal blood flow to working muscle during exercise appears to be confined to oxidative working muscle.[4] This impaired metabolic vasodilatory capacity within skeletal muscle in patients with chronic heart failure during exercise has often been attributed to excessive sympathetically mediated vasoconstriction, activation of the plasma renin–angiotensin system, and, more recently, to increased levels of endothelin. Although these neutral and neurohumoral factors can exert potent systemic and regional vasoconstriction, they do not

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completely explain the impaired vasodilating capacity within skeletal muscle in patients with chronic heart failure. The early work of Zelis et al,[5] recently confirmed by Le Jemtel et al[6] (for large muscle mass in exercising leg), indicates that this impaired metabolic vasodilation during exercise cannot be restored by α-adrenergic blockade with phentolamine.

EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS ON SKELETAL MUSCLE FLOW

Angiotensin-converting enzyme (ACE) inhibition does not restore impaired metabolic vasodilation after acute administration, despite a substantial reduction of plasma angiotensin II and norepinephrine levels.[7] This indicates that blockade of the plasma renin–angiotensin system by ACE inhibitors does not interfere with blood flow to working muscle during exercise in patients with CHF.[7,8] However, after chronic treatment with an ACE inhibitor over 3 months, a significant increase in femoral blood flow was noted during exercise and was accompanied by improved peak oxygen consumption.[7] Thus, it appears that chronic ACE inhibitor therapy reversed the inability of peripheral vessels to dilate. In fact, these findings are consistent with previous observations of the delayed beneficial effect of ACE inhibitors in large-scale trials,[9] indicating that the full beneficial effect of ACE inhibitors emerges slowly over time.

What is the explanation for the temporal dissociation between the rapid improvement in hemodynamics and gradual improvement in exercise performance? Obviously, exercise tolerance in patients with heart failure appears not to be solely determined by central hemodynamics. It is tempting to speculate that the delayed effect of ACE inhibitors may be, in part, due to interference with the vascular tissue renin–angiotensin system, thereby reversing chronic structural alteration of the vessel. Experimental evidence indicates that angiotensin II induces hypertrophy of cultured rat aortic smooth muscle cells.[10] Angiotensin II and possibly endothelin and norepinephrine appear to be involved in the activation of proto-oncogenes. This suggests that angiotensin II may be involved in the proliferative process of tissues during growth (endogenous growth factor). Recent observations indicate that ACE inhibition can reverse structural vascular alteration in a rat model of hypertension[11] and these beneficial vascular effects appear to be more prominent with ACE inhibitors than other antihypertensive drugs.[12]

ENDOTHELIAL DYSFUNCTION

Recent data from our laboratory and others[13-15] demonstrated that endothelium-dependent relaxation of the skeletal muscle microcirculation in response to acetylcholine is impaired in chronic heart failure, whereas the vasodilating effect of nitroglycerin is preserved. There is experimental evidence that long-term treatment with ACE inhibitors restores endothelial dysfunction in hypertensive rats.[16] This beneficial effect of ACE inhibitors on endothelial function is most likely due to the inhibition of the breakdown of bradykinin, which is degraded by ACE.[17] This mechanism may increase local tissue levels of bradykinin, which, in turn, stimulates the release of nitric oxide (which accounts for the biologic activity of the endothelium-derived relaxing factor, EDRF) and vasodilating prostaglandins.[17,18] This pathway (Figure 1) may also have important long-term effects in that nitric oxide may inhibit mitogenesis and proliferation of vascular smooth muscle cells. Other potential mechanisms involved in the impaired metabolic peripheral dilation in chronic heart failure include a vascular stiffness component owing to the increased vascular sodium content, which can be reduced with diuretic therapy in decompensated heart failure.[19]

INTRINSIC ALTERATIONS OF SKELETAL MUSCLE IN CHRONIC HEART FAILURE

Although acute administration of some vasodilators or positive inotropes has been shown to improve blood flow to skeletal muscle during exercise, exercise duration and maximal oxygen consumption did not increase immediately after administration of these drugs,[20] indicating that oxygen

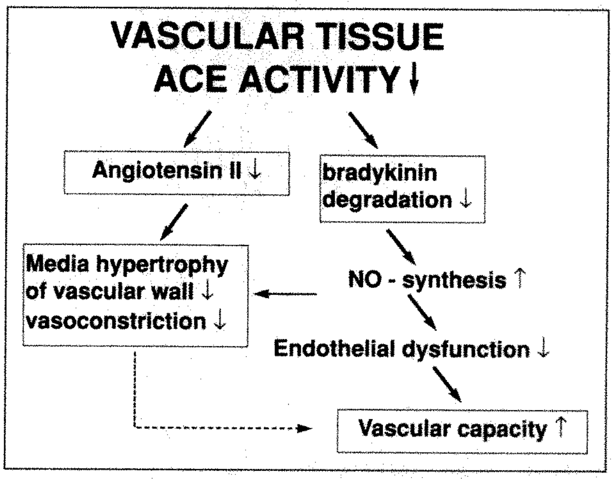

FIGURE 1. Proposed mechanism by which angiotensin-converting enzyme (ACE) inhibitors may improve endothelial function and vascular remodeling (see text for explanation). NO = nitric oxide.

uptake of skeletal muscle during exercise cannot be improved in patients with chronic heart failure, even when oxygen delivery is enhanced. This observation suggests shunting of blood flow away from active muscle or intrinsic alterations of skeletal muscle in chronic heart failure, or both. We have noted previously that there might be a shift from oxidative skeletal muscle to activation of more glycolytic working muscle fibers,[4] again indicating a change in the properties of the skeletal muscle itself. Histologic examination of skeletal muscle from patients with chronic heart failure revealed atrophy and increased interstitial cellularity as well as biochemical alterations of the skeletal muscle.[21] Ultrastructural analysis of skeletal muscle biopsy specimens has shown a reduced oxidative capacity of the muscle, as indicated by a reduced volume density and reduced surface area of the cristae of mitochondria.[22] These findings were even more striking with cytochrome c oxidase staining of ultrastructural and light microscopy material (Figure 2). In fact, a close relation has been found between the oxidative capacity of working muscle (as assessed by cytochrome c oxidase; Figure 3) or volume density of mitochondria within the skeletal muscle[22] and the peak oxygen consumption during exercise. Thus, exercise capacity appears to be, in part, determined by the condition of the working muscle.[23]

Previous studies have documented that the relation of maximal oxygen consumption and oxidative capacity of working muscle holds true when

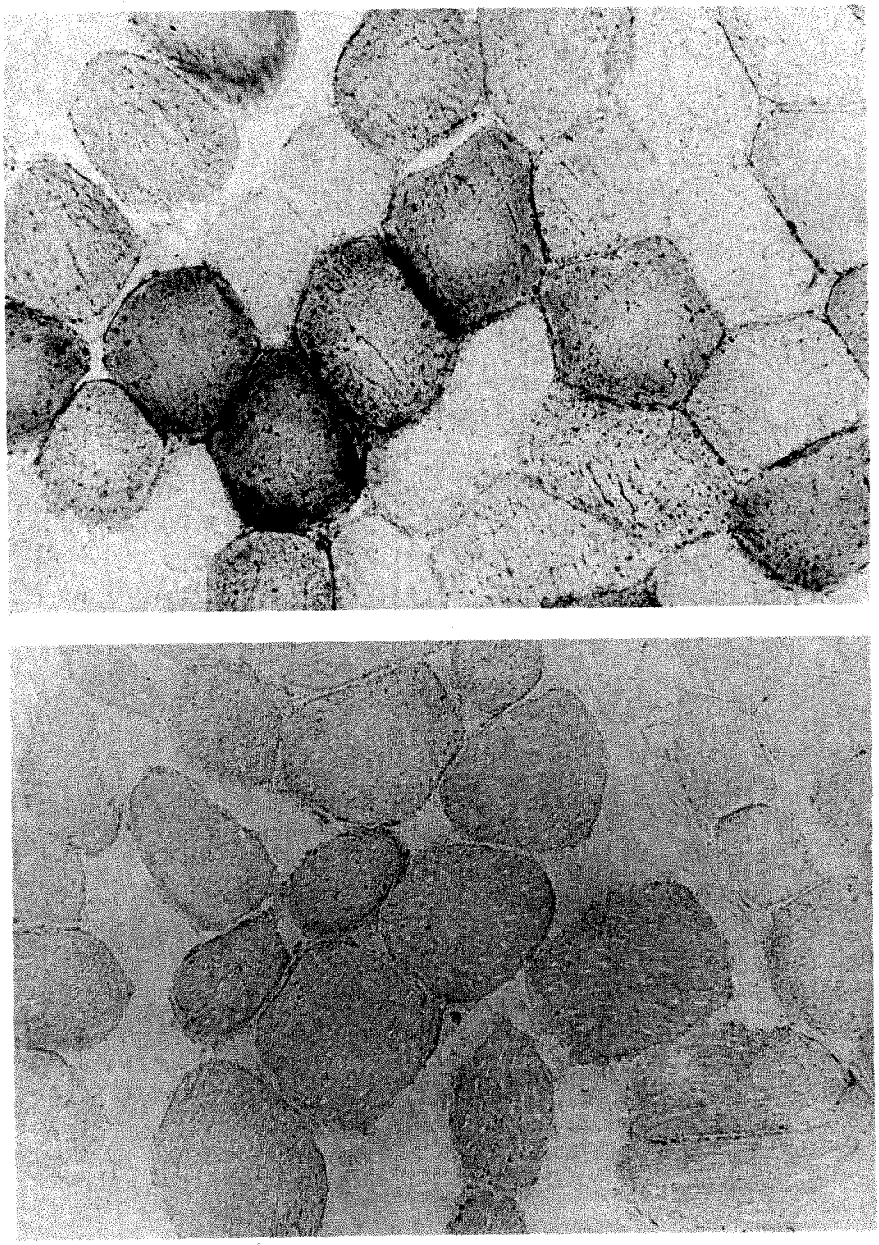

FIGURE 2. Light microscopy of skeletal muscle after staining of the cytochrome c oxidase, an oxidative enzyme within the mitochondria (black staining). *Top*: normal subject; *Bottom*: patient with severe heart failure. The cytochrome c oxidase is reduced in all fibers of patients with heart failure, but more markedly so in oxidative fiber types.

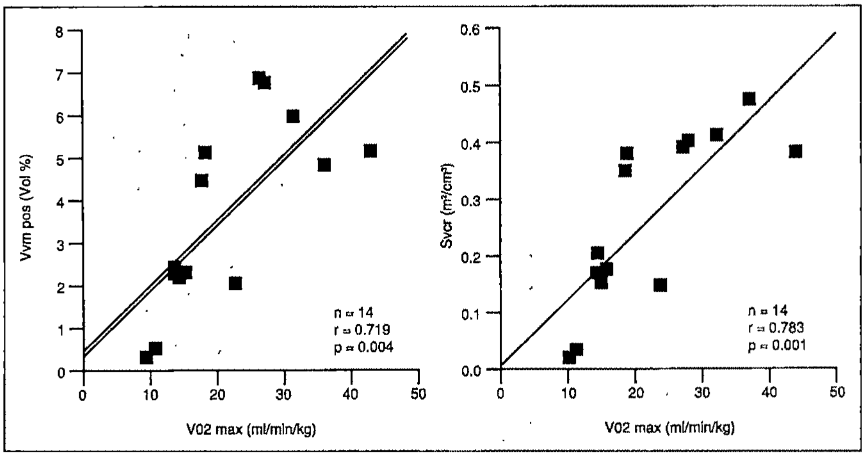

FIGURE 3. Relationship of peak oxygen consumption during exercise (VO2 max) and the volume density of cytochrome c oxidase-positive mitochondria (*left*; Vvm pos; vol % refers to percentage of total muscle volume) and surface density of cristae of cytochrome c oxidase-positive mitochondria (Svcr m²/cm³).

investigating the oxidative capacity of skeletal muscle of sedentary and exercise-trained persons.[24,25] Recent experimental studies indicate that the muscles' aerobic capacity is proportional to maximal oxygen consumption.[26] The biochemical analyses of skeletal muscle are consistent with our ultrastructural analysis: i.e., enzymes involved in aerobic metabolism (e.g., succinate dehydrogenase or citrate synthetase) were reduced in patients with chronic heart failure.[27,28] The pattern (obtained by nuclear magnetic resonance spectroscopy) revealed abnormal metabolism in skeletal muscle,[29] supporting the ultrastructural and biochemical observations. Using nuclear magnetic resonance, it was demonstrated that the intracellular pH values during exercise are much lower (consistent with increased lactate) for a given work load in patients with severe heart failure. Moreover, during exercise, the plasma concentrations of inorganic phosphate and phosphocreatinine decreased much faster in patients with heart failure than in normal persons.[29,30]

The impact of impaired blood flow during exercise on these skeletal muscle alterations remains controversial. Subsequent studies utilizing nuclear magnetic resonance spectroscopy as well as skeletal muscle function tests in patients with chronic heart failure have suggested that the abnormalities are not related to different rates of blood flow to working muscle during exercise.[31-33] However, in terms of reduced blood flow as a contributing mechanism, it is conceivable that skeletal muscle ischemia during exercise may be associated with (or even trigger) mitochondrial adaptations. Thus, repeated episodes of reduced blood flow within skeletal muscle may be involved in the development of skeletal muscle alterations, despite the fact that these alterations, once developed, can be demonstrated in the absence of any correlation with blood flow measured during the assessment of muscle function[33] or metabolism.[31,32] Indeed, we found a significant correlation between skeletal muscle blood flow during exercise and mitochondrial volume density, which supports the notion that chronically reduced blood flow during exercise might be involved in terms of skeletal muscle abnormalities (Figure 4). Since the quantitative assessment of mitochondrial volume density and the surface density of cristae represents the structural correlate of the oxidative capacity, these correlations (Figure 4) would support the notion that chronically reduced blood flow to skeletal

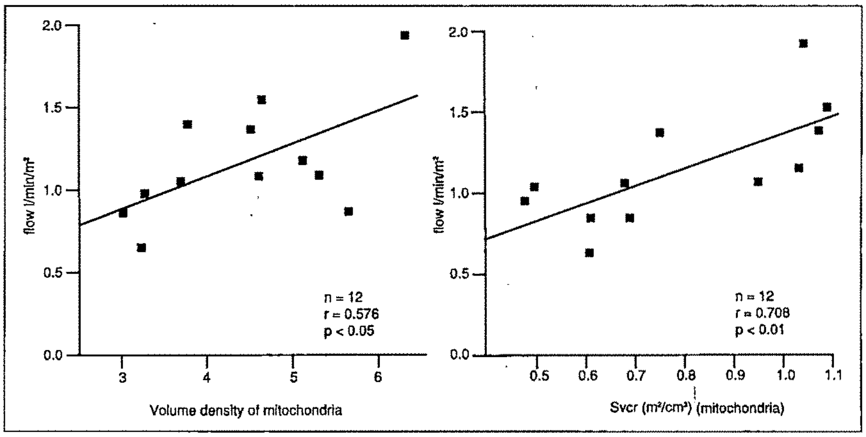

FIGURE 4. Relation of skeletal muscle blood flow during peak exercise (flow; liters/min/m²) and volume density of mitochondria (*left*; vol %) and surface density of cristae (*right*; Svcr m²/cm³).

muscle during exercise might be involved in the pathophysiology of skeletal muscle abnormalities in this setting.

Regardless of the potential underlying mechanisms, there is evidence that these peripheral alterations of skeletal muscle are reversible with effective therapy.[22] Treatment with ACE inhibitors increases femoral oxygen extraction after long-term therapy,[7] and preliminary data from our laboratory suggest that this effect is accompanied by an increase in volume density of skeletal muscle mitochondria, as assessed by repeated skeletal muscle biopsies. This would suggest that long-term ACE inhibition improves oxidative capacity of working muscle and, thereby, in addition to the long-term improvement in femoral blood flow, contributes to the overall improvement in exercise capacity of these patients.

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Angiotensin-Converting Enzyme Inhibitors, Left Ventricular Dysfunction, and Early Heart Failure

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A study was undertaken to examine the effects of the angiotensin-converting enzyme inhibitor lisinopril on exercise performance in 18 patients with major impairment of left ventricular systolic function. The study was a randomized, double-blind, crossover design, and patients received treatment with either once-daily lisinopril (2.5–10 mg) or placebo for a period of 6 weeks. A total of 15 patients completed the study. Compared with placebo, lisinopril had no significant effect on supine or standing blood pressure or heart rate. Although lisinopril had no effect on exercise duration during a low-intensity exercise protocol, in patients undergoing a high-intensity exercise protocol, there was a trend toward improved exercise time and peak oxygen consumption improved significantly. In addition, treatment with lisinopril resulted in an increase in renal blood flow and a reduction in glomerular filtration rate. Moreover, administration of once-daily lisinopril 10 mg resulted in a decrease in plasma concentrations of angiotensin II, aldosterone, and atrial natriuretic peptide, and an increase in plasma concentrations of active renin.

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Angiotensin-converting enzyme (ACE) inhibitors, in conjunction with diuretic agents, have an established role in the management of moderate and severe heart failure due to left ventricular dysfunction.[1–5] Among patients already receiving diuretics, addition of an ACE inhibitor improves prognosis and (in patients suffering from dyspnea despite such treatment) symptoms and exercise performance improve.[1–5]

Patients with asymptomatic left ventricular dysfunction exhibit little or no increase in plasma concentrations of angiotensin II and aldosterone whereas in patients with heart failure treated with small doses of diuretics, levels are only modestly elevated.[6–12] It is not yet clear if ACE inhibitors will benefit patients with milder forms of heart failure, and, if they do, the mechanism by which they would exert improvement is not clear.

The goals of management in mild, compared with moderate or severe, heart failure are somewhat different (Figure 1). The survival of patients with heart failure is broadly related to the severity of their condition. Although the sickest patients have the worst prognosis, the primary goal of management is still the relief of symptoms. In milder degrees of heart failure, in which symptoms are often well controlled by diuretics alone, the primary goals of management are to prevent or retard deterioration to the more severe degrees of heart failure and to improve survival.

However, survival is also closely related to the severity of ventricular function, measured either at rest using imaging techniques or during exercise using oxygen consumption.[13,14] Patients with mild heart failure have impaired exercise tolerance, even if their symptoms are controlled by diuretic therapy. Likewise patients with asymptomatic left ventricular dysfunction also have impaired exercise tolerance and peak exercise oxygen consumption.[15] Some patients avoid developing symptoms by restricting their activity, whereas others fail to report symptoms, despite evidence of major cardiac dysfunction. Accordingly, exercise testing may be

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usefully employed to quantify the severity of impairment in cardiac reserve and the impact of therapy.

In the present study we examined the effect of a long-acting ACE inhibitor, lisinopril, on exercise performance in a group of patients without symptoms but with major impairment of left ventricular systolic function. Peak oxygen consumption was measured to determine changes in cardiac reserve. Since there is as yet no information on the effects of ACE inhibition on neuroendocrine, metabolic, or renal function in patients with left ventricular dysfunction not receiving diuretic therapy, detailed assessments were made in order to explain any changes in clinical status.

METHODS

Patients: Eighteen men, mean age 58 years, with minimal or no symptoms of heart failure but with echocardiographic evidence of major left ventricular dysfunction (estimated ejection fraction <40%) were identified. Prior to the screening visit for inclusion in the study, 1 patient died unexpectedly during sleep. The mean left ventricular ejection fraction measured by radionuclide ventriculography was 39.9% at baseline in the remaining 17 patients who participated in the study. All patients had a history of a previous myocardial infarction that had affected the anterior, inferior, or both territories in 10, 3, and 4 patients, respectively; no patient had had a myocardial infarction within 1 year of the study. Eleven had had coronary revascularization performed, but none within 6 months of the study. The right atrial appendage had not been removed at the time of operation in any patient. No patient had evidence of reversible ischemia or evidence of significant mitral regurgitation. Patients were excluded if they were receiving a diuretic or other cardioactive medication, or had significant pulmonary or systemic disease. All patients were in sinus rhythm.

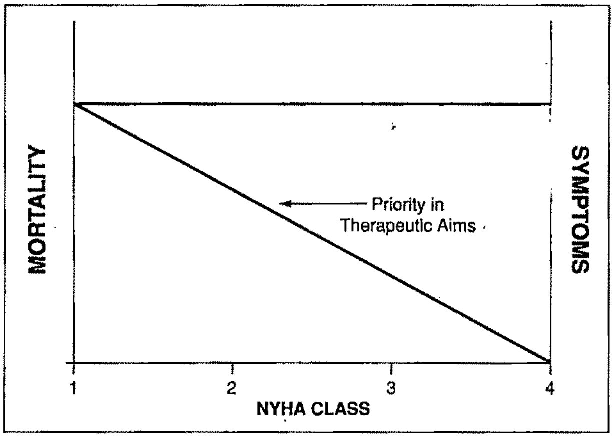

FIGURE 1. Relative importance of symptoms and prognosis in the management of heart failure. In mild heart failure symptoms are not prominent, improving survival is the primary goal of therapy. In severe heart failure control of symptoms is of paramount importance even though the prognosis is poor. NYHA = New York Heart Association.

Study design: After agreeing to participate, patients were placed on a metabolic diet containing 100 mmol of sodium and 40 mmol of potassium for 3 days prior to the baseline tests. Venous samples were taken with the patient in the supine position for measurement of plasma concentrations of renin, angiotensin II, aldosterone, antidiuretic hormone, catecholamines, and atrial natriuretic peptide.[3,4,16]

Ventricular function at rest was assessed by Doppler and 2-dimensional echocardiography and gated blood pool scanning. Exercise performance was assessed by using 2 exercise tests of different intensity. Oxygen consumption was measured during the high-intensity protocol. All patients underwent familiarization with at least 2 exercise tests prior to inclusion in the study. Renal function and the metabolic effects of lisinopril were assessed by radionuclide studies[17] and serial estimation of serum urea, electrolytes, and creatinine.

Subsequently, patients entered a randomized, double-blind, crossover study with 6-week treatment periods comparing lisinopril and matching placebo. Each patient received an initial dose of 2.5 mg lisinopril or placebo at the start of each phase of the study and was monitored for 6 hours thereafter. Patients then received lisinopril 5 mg/day or matching placebo for 2 weeks. If the patient tolerated this dose and the systolic blood pressure was >100 mm Hg, the patients then received lisinopril 10 mg/day or matching placebo for the remaining 4 weeks.

Statistical analysis: Values given are mean ± standard deviation where data are normally distributed. Mean, median, and range are quoted where data are not normally distributed.

Variables were first tested for order and/or period effects; if found, that variable was excluded from further statistical analysis. The changes from baseline to the end of each treatment phase were compared. Student's t test was used with prior logarithmic transformation of the data if they were not normally distributed.

RESULTS

Clinical outcome: Fifteen patients completed the study. One patient decided not to participate further after completing the baseline tests. One patient who completed the first 6 weeks of the study receiving lisinopril was assessed and started the second 6-week course receiving placebo. He developed dizziness while receiving placebo and stopped therapy some days prior to the 2-week visit and was excluded from analysis.

No patient developed symptomatic hypotension after the first dose of lisinopril and all patients progressed to the higher dose of lisinopril.

Baseline study results: At baseline, despite lack of symptoms, exercise performance was impaired. Plasma concentrations of active renin, angiotensin II, aldosterone, or norepinephrine were not elevated, but plasma concentrations of atrial natriuretic peptide were. Renal blood flow and glomerular filtration rate were well preserved (Table I).

Effects of lisinopril: The systolic and diastolic blood pressure at baseline (mean ± standard deviation) were 139 ± 13 and 82 ± 5 mm Hg, respectively. Compared with placebo, lisinopril had no effect on supine or standing blood pressure at rest or resting heart rate.

Lisinopril did not affect exercise duration during the low intensity protocol. Patients stopped for a variety of reasons during this protocol, mainly breathlessness or fatigue. However, with the high intensity protocol, peak oxygen consumption was greater during treatment with lisinopril than placebo ($p < 0.01$), this was associated with a trend toward improved exercise time ($p = 0.09$). The major limiting symptom during this test was breathlessness (Figures 2 and 3)

Treatment with lisinopril resulted in an increase in renal blood flow and a reduction in glomerular filtration rate (Figure 4).

Treatment with once-daily lisinopril 10 mg resulted in a decrease in the plasma concentrations of angiotensin II, aldosterone, and atrial natriuretic peptide, whereas plasma concentrations of active renin increased.

DISCUSSION

What is mild heart failure?: Studies in mild heart failure are beset by the problems of defining the presence and severity of heart failure. Thus, in both the recently reported Studies of Left Ventricular Dysfunction (SOLVD; treatment arm) and Second Vasodilator–Heart Failure Trial (VHeFT-II) studies,[18,19] the mean peak oxygen consumption was < 14 mL/kg/min, a level at which some centers would suggest that cardiac transplantation should be implemented.[20]

TABLE I Baseline Study Results

Variable	Result [Mean (Range)]	Normal Range
Peak VO_2	20.8 (14–27.6)	>25
Plasma ARC (μU/mL)	16 (1–45)	10–50
Plasma angiotensin II (pmol/liter)	12.0 (4–36)	5–35
Plasma aldosterone (pg/mL)	112 (25–303)	15
Plasma ANP (pg/mL)	64 (6–187)	5–50
Plasma norepinephrine (nmol/liter)	2.1 (0.9–3.9)	0.8–3
Plasma epinephrine (nmol/liter)	0.2 (0.1–0.4)	ud–0.2
Plasma ADH (pg/mL)	1.1 (0.2–4.6)	0.3–0.7

ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; ARC = active renin concentration; ud = undetectable; VO_2 = oxygen consumption.

The disparity between the severity of ventricular dysfunction measured at rest and symptoms and exercise performance highlight the difficulties of defining mild heart failure.[21,22] Some patients will have severe ventricular dysfunction but only mild symptoms; others have severe symptoms and require high doses of diuretic without major ventricular dysfunction. Commonly, the term mild heart

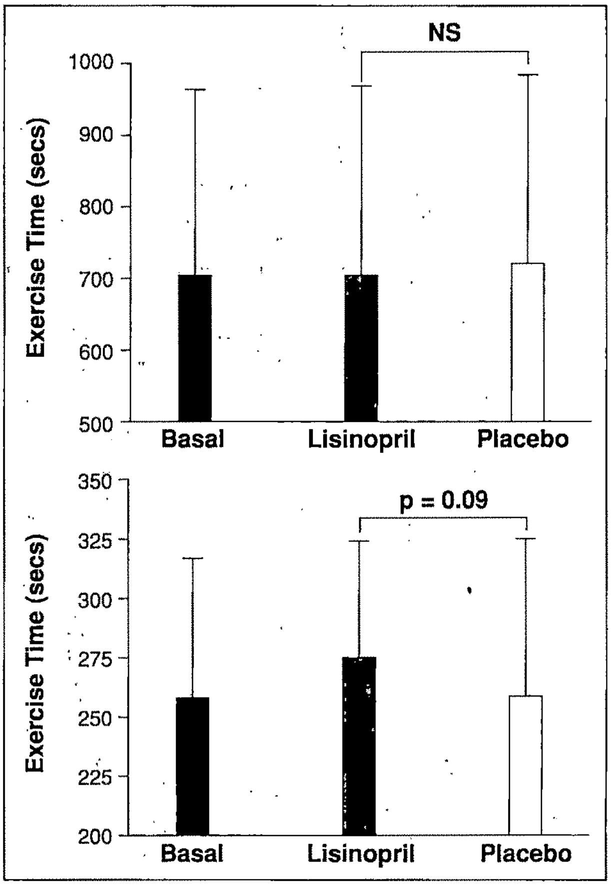

FIGURE 2. Exercise performance using the low intensity protocol (*top*). No significant difference noted between placebo and lisinopril. Exercise performance using a high intensity protocol (*bottom*). Patient exercised for longer during treatment with placebo and the treatment difference approached statistical significance.

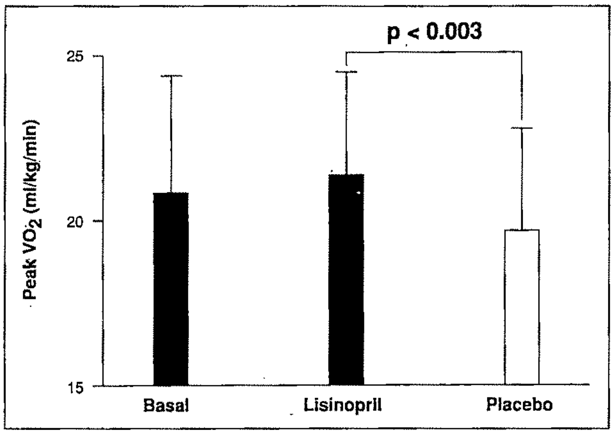

FIGURE 3. Peak oxygen consumption (VO_2) during the high intensity protocol. Peak oxygen consumption was significantly higher on lisinopril compared with placebo.

failure is used to mean ventricular dysfunction with symptoms of breathlessness or fatigue only on moderate or severe exertion, whereas many would add that the patient should not be on a large dose of diuretic. Although the prognosis is generally better in patients with milder symptoms, this may not be true for the subgroup with severe ventricular dysfunction.

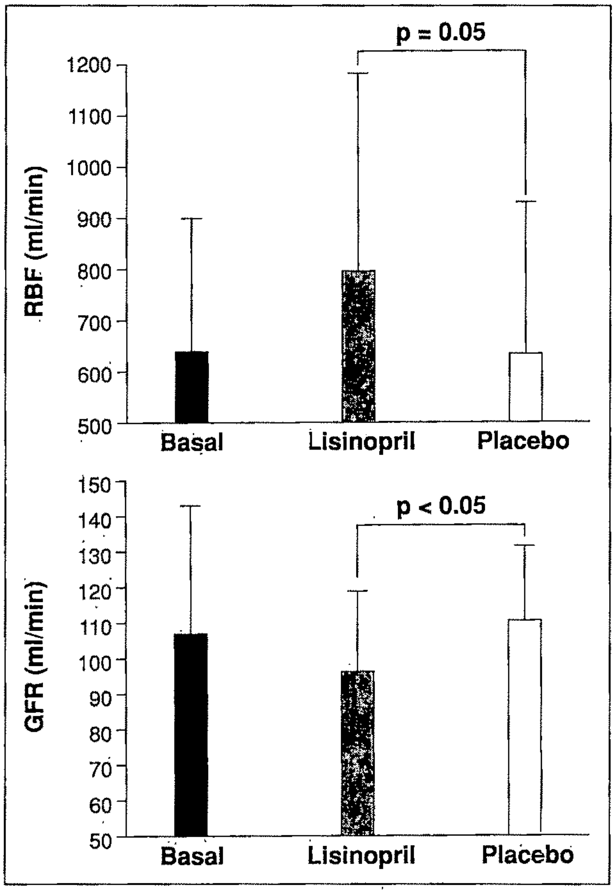

FIGURE 4. Renal blood flow (RBF) was measured using a first-pass radionuclide technique (*top*). Renal blood flow increased significantly during treatment with lisinopril compared with placebo. Glomerular filtration rate (GFR) measured by a radioisotopic technique, fell slightly during treatment with lisinopril (*bottom*).

The reasons why there is a disparity between symptoms and the severity of ventricular dysfunction are undoubtedly complex. Some measures of function frequently used as "gold standards" are probably inaccurate, such as the thermodilution catheter[23]; others, such as the left ventricular ejection fraction, are critically dependent on such other measures as ventricular volume in diastole for their proper interpretation. Resting ventricular function is a poor predictor of how the heart will behave during exercise,[21] which is when symptoms occur. Symptoms will also vary depending on precisely what question the patient is asked and how it is interpreted by the investigator,[22,24,25] which makes comparisons between centers difficult.

Study endpoints in patients with mild heart failure and asymptomatic left ventricular dysfunction: The problems of defining mild heart failure are compounded by the difficulty in measuring valid endpoints. Because symptoms are not a major feature of mild heart failure and by definition are absent in asymptomatic left ventricular dysfunction, they are a poor guide to the effectiveness of treatment. It could also be argued that if symptoms are well controlled, further treatment cannot improve matters. Nonetheless, detailed surveys do detect a considerable reduction in the quality of life even at this early stage.[26] This may reflect patient denial or that the doctor has not probed deep enough when classifying a patient as mild or asymptomatic.

The extent of ventricular dysfunction measured at rest has been shown to predict subsequent mortality in patients with heart failure both of ischemic and nonischemic origin.[27,28] An agent that improves resting ventricular function might favorably influence outcome.

Exercise performance is reduced in the presence of ventricular dysfunction, even in the absence of symptoms. Most people rarely exercise to their cardiorespiratory maximum, so it is not surprising that cardiac reserve may be considerably reduced before the onset of symptoms. In patients with overt heart failure some studies have shown a relation between prognosis and exercise performance or peak oxygen consumption.[13,14] Improving the cardiac reserve might delay progressive deterioration in ventricular function, allow the patient to survive further acute cardiac insults, and could even reduce the chance of sudden death.

The rationale for treating mild heart failure inevitably requires some extrapolation from severe heart failure. In patients with moderate-to-severe heart failure, increases in the neuroendocrine activity have been associated with a worse prognosis.[29–31] It is uncertain whether this merely reflects a general disruption of neuroendocrine homeostasis, signaling a cardiovascular system in difficulty, or whether neuroendocrine activation contributes directly to increased mortality. Elevated plasma concentrations of atrial natriuretic peptide and plasma norepinephrine are associated with increased atrial pressure and low arterial pressures, respectively,[14,16,30] both of which are clinical markers of a worse prognosis in heart failure. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[5] has indicated that it is those patients with strikingly elevated concentrations of neuroendocrine markers who have the greatest benefit in terms of prognosis with the use of an ACE inhibitor.[31] Angiotensin II and catecholamines may produce myocyte necrosis in concentrations found in heart failure, and it is possible that gradual neuroendocrine-mediated myocyte destruction is responsible for the progression of ventricular dysfunction.[32,33] Patients with markedly activated neuroendocrine systems have more potassium depletion and more arrhythmias, both of which can be reversed by ACE inhibition.[3,4,34,35] This may improve prognosis by reducing sudden death.

By contrast, studies in patients with chronic left ventricular dysfunction and mild chronic heart failure, untreated with diuretics, show little activation of the renin–angiotensin system, although increases in plasma norepinephrine and atrial natriuretic peptide are fairly consistent.[6–11] Theoretically, at least, it may be advantageous to reduce neuroendocrine activity further, using an ACE inhibitor, rather than activate the renin–angiotensin system with a diuretic.[7] Reduction of atrial natriuretic peptide (in the absence of an atrial peptidase inhibitor) reflects a reduction in atrial pressure and may be achieved by either an ACE inhibitor or a diuretic.[36] In patients with mild heart failure, the ability to withdraw established diuretic therapy under suitably controlled circumstances is a marker of therapeutic efficacy.

Ultimately, the most important markers of efficacy in treatment of heart failure are reduction in progression to more severe heart failure and reduction of premature sudden death. These endpoints can only be addressed in large studies.

A review of studies in mild heart failure: There is only one well conducted randomized study in mild heart failure that has compared the effects of an ACE inhibitor with placebo on symptoms and exercise response. The captopril/digoxin multicenter study[37] revealed that the ACE inhibitor improved exercise time and symptoms compared to placebo, an effect that was not observed with digoxin. Most of the patients in this study were receiving diuretics. There was also evidence that the ACE inhibitor could reduce ventricular arrhythmias in this setting.

The CONSENSUS, V-HeFT-II, and SOLVD (treatment) studies have reported that the ACE inhibitor enalapril reduces the mortality in patients with severe and mild or moderate degrees of heart failure. Although no significant reduction in mortality was observed in patients with asymptomatic ventricular dysfunction in the prevention arm of SOLVD, a delay in onset and possibly prevention of heart failure was observed in those treated with enalapril. Kleber and Doering[38] report that captopril also retards progressive ventricular dysfunction, suggesting that the benefits of ACE inhibitors are a class effect.

How ACE inhibitors reduce mortality remains controversial and subject to reporting bias. The SOLVD study suggested that the major impact of ACE inhibitors on mortality was by retarding the progression of ventricular dysfunction, but sudden death in the setting of worsening heart failure was inappropriately classified as due to progressive heart failure in this study. The V-HeFT-II study suggested the predominant effect of enalapril was on sudden death. Preliminary data from Survival and Ventricular Enlargement (SAVE), using captopril in patients with poor ventricular function after myocardial infarction, indicate a reduction in progressive ventricular dysfunction and sudden death. Intriguingly, both SOLVD and SAVE noted that ACE inhibitors substantially reduced recurrent myocardial infarction, suggesting an antiatherosclerotic effect, despite their potential to exacerbate exercise-induced angina.

A study by Richardson et al[39] compared captopril versus furosemide 40 mg and amiloride 5 mg combination in 15 patients with heart failure who had little or no symptoms on furosemide in doses up to 80 mg/day. Four patients developed acute pulmonary edema when taking captopril alone, all of whom had previously had an episode of pulmonary edema. In the remaining 11 patients no clinical difference was noted between the 2 treatments. This suggests that in patients who have exhibited signs of frank fluid retention an ACE inhibitor alone is not effective therapy. Despite many ex cathedra statements, there is little evidence that ACE inhibitors cause a negative fluid balance; rather the reverse is true, at least in the short term.

In a study by Kromer and Riegger,[40] patients with heart failure were treated with the ACE inhibitor quinapril or matching placebo. About 20% of the patients were not receiving a diuretic. Nonetheless, these patients improved their exercise performance as much as those patients receiving diuretics. This suggests that diuretics are not a necessary concomitant therapy in order for ACE inhibitors to demonstrate their clinical benefits.

Dickstein et al[15] recently reported a study of the effects of enalapril on exercise performance in 160 men who had had a myocardial infarction. The patients had mild exercise intolerance without effort angina and all were treated with a β-blocker after the infarction. The study failed to demonstrate a difference between placebo and enalapril on exercise performance or peak oxygen consumption over the following year.

Studies that compare ACE inhibitors to other active therapies in patients with mild heart failure are open to interpretation. Most have compared an ACE inhibitor to digoxin. These have indicated variously that the ACE inhibitor is equivalent to or only slightly better than digoxin.[41,42] The balance of evidence suggests that although digoxin has long-term positive inotropic activity,[37] it can generally not be distinguished from placebo in terms of its effects on exercise performance or symptoms in mild heart failure.[43,44] Demonstration of equivalence of digoxin and an ACE inhibitor could be interpreted as showing a lack of effect of either agent.

The present study demonstrates that lisinopril can improve peak oxygen consumption in patients with left ventricular dysfunction and impaired exercise tolerance, indicating that ACE inhibitors can improve cardiopulmonary reserve before the onset of heart failure. Lisinopril did not improve exercise tolerance during a low intensity protocol. This is consistent with the evidence that low intensity protocols, while simulating usual daily activity better, are less likely to provoke a maximum cardiopulmonary effort in patients with ventricular dysfunction.[22,24] This is reflected in the symptom-limiting exercise. Patients exercised using high intensity protocols are more likely to stop due to breathlessness, whereas patients exercised with a low intensity protocol stop for a variety of reasons.[24]

The reasons why exercise performance improved are not clear. Patients with evidence of reversible ischemia were carefully excluded because ACE inhibitors have been shown to exacerbate exertional angina,[45] at least when used in combination with diuretics. The patients in the study by Dickstein et al[15] also had angina as an exclusion criterion, but all the patients were receiving β blockers, which could have prevented any beneficial effect of enalapril. As they were taking a β blocker, the patients in the Dickstein et al[15] study probably had lesser underlying impairment in exercise performance than in the present study. The fall in plasma concentrations of atrial natriuretic peptide indicate that left ventricular filling pressures were reduced, at least at rest. Reductions in plasma concentrations of angiotensin II may have led to a reduction in vascular resistance, although lisinopril exerted no effect on arterial pressures. ACE inhibitors correct intracellular potassium deficits in patients with heart failure treated with diuretics, and this may be responsible for the reduction in fatigue and an improvement in skeletal muscle performance during exercise.[46] However, it is not known whether the potassium deficit in heart failure precedes the introduction of diuretics. This is possible, as increases in atrial natriuretic peptide and catecholamines could cause potassium deficits,[47,48] and potassium deficit is better related to neuroendocrine activation than diuretic dose in heart failure.[34]

As in patients with overt heart failure on diuretics, lisinopril caused an increase in renal blood flow[3,4,49,50] and reduction in glomerular filtration rate.[3,4,49,51] The influence of the changes in renal hemodynamic function on salt and water homeostasis have yet to be addressed but an improvement could be an additional mechanism by which patients derive benefit from ACE inhibitors.

CONCLUSION

Lisinopril improves cardiopulmonary reserve in patients with impaired ventricular function. This could lead to a delay in the onset of overt heart failure and improve prognosis both by reducing sudden death and progressive heart failure. The mechanisms by which patients derive benefit from treatment with ACE inhibitors in the absence of a diuretic when activity of the circulating renin–angiotensin system is low remains to be elucidated. Speculation of a potential role of independently regulated tissue renin–angiotensin systems is premature.

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GISSI-3 Study Protocol on the Effects of Lisinopril, of Nitrates, and of Their Association in Patients with Acute Myocardial Infarction

GISSI-3-Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico

The role of thrombolysis in the acute phase of myocardial infarction (AMI) has been definitely established in terms of mortality and ventricular function, as has the equivalence of different thrombolytic agents. The Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trial showed that a large number of patients have either clinical heart failure or severe left ventricular damage on discharge from the hospital, with a large risk of death and poor prospects in terms of quality of life. Additional measures to limit ventricular damage are therefore essential to reducing morbidity. The GISSI-3 study protocol on the effects of lisinopril and nitrates, used alone or in combination, in patients with AMI is described in detail.

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The protocol presented here became standard practice within the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI) group in June 1991, following a pilot phase that involved 1,500 patients.

THE PILOT STUDY

A pilot study of the experimental treatments proposed for the GISSI-3 trial was required because no hard body of data from phase II trials was available to provide reliable indications on the treatments' pharmacodynamic effects in the early acute phase of myocardial infarction or on the adverse effects to be expected as a result of the administration of hypotensive drugs in a period of serious circulatory instability.

It was believed that the context provided adequate conditions for experimenting with a new approach to the traditional concept of the pilot phase. The philosophy of the GISSI trials rests on the participation of a majority of the coronary care units in the country, in which the "intensity" of clinical monitoring may be expected to be highly variable. Thus, instead of limiting the controlled observation of the regimens to be used in the main trial to a restricted number of selected centers and patients, it was decided to launch a pilot trial involving all candidate centers, using the same recruitment and management criteria devised for the main trial, with the important exception of a very strict scheme for blood pressure monitoring in the first 72 hours.

The results of this strategy are summarized in Figure 1. From January to March 1991, 1,500 patients were enrolled. The data of the intensive early monitoring phase was sent by fax to the coordinating center, for the real-time surveillance of the pattern of distribution of persistent (≥ 1 hour) hypotensive episodes. The data were forwarded in parallel to the Data Monitoring Committee and to the Steering Committee to obtain their

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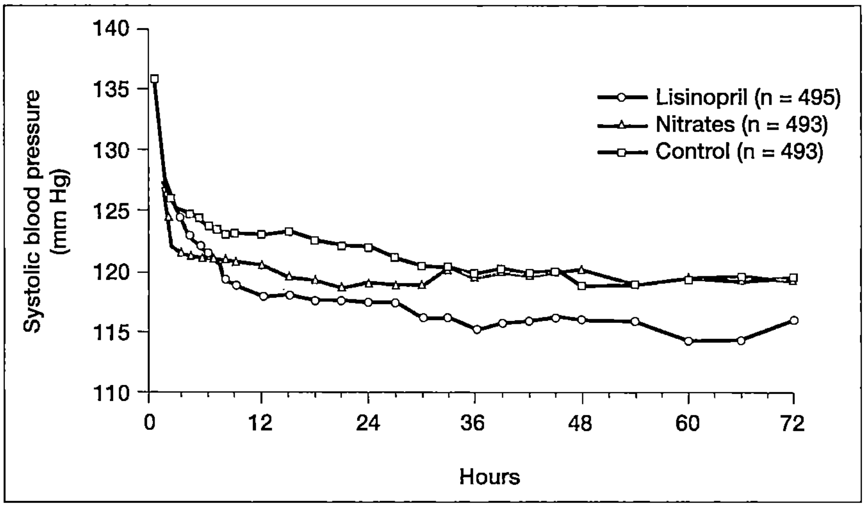

FIGURE 1. GISSI-3 pilot study showing the 72-hour systolic blood pressure profile in the overall population.

opinions on the safety aspects of the protocol applied in the routine conditions of care.

The findings were eventually presented to the assembly of investigators to allow a fully informed discussion of the findings and of their implications for the management of the main trial prior to its inception, with a special focus on subgroups at particular (expected) risk as a result of the early hypotensive intervention.

The results of the pilot phase shall be described in detail elsewhere; no major problems occurred, and the slight amendments introduced in the protocol were seen by the investigators as "natural" adjustments of the original proposal.

Due to the important support of this educational and informative exercise, the main trial was able to start with a high degree of confidence. The recruitment rate of the first months has indeed been promising (Figure 2), and the study can reasonably be expected to reach its recruitment goal in 18–20 months as anticipated.

The publication of the study protocol is in response to the increasing need for clarity in the field of clinical trials. Although similarities with the parallel Fourth International Study of Infarct Survival (ISIS-4) trial are indeed conspicuous—for once again the 2 groups have proceeded independently in the same direction[1]—some important differences should be stressed. These mainly relate to the inclusion in the GISSI strategy of assessment of ventricular function embodied in the main endpoint. A 2-stage evaluation, at 6 weeks and at 6 months—suggested by and discussed with the U.S. Food and Drug Administration—was oriented to ascertainment of the experimental treatments' efficacy in prevention of severe ventricular dysfunction, in addition to measuring the impact of the treatments on mortality.

GENERAL BACKGROUND TO THE GISSI-3 PROTOCOL

The role of thrombolysis in the acute phase of myocardial infarction (AMI) can be considered to be definitely established in terms of mortality and ventricular function, and the ISIS-3 study[2] has confirmed the GISSI-2 results[3] with respect to the equivalence of different thrombolytic agents.

Thrombolytic treatment, together with aspirin and β blockers, should be given to all patients with an AMI diagnosed within the first 12 hours after the onset of symptoms. The broadening of the time window has been justified by the potential benefit suggested by the meta-analysis of the results of GISSI-1,[4] ISIS-2,[5] ISIS-3,[2] and the Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS)[6] for patients randomized 6–12 hours after AMI.

The findings of the GISSI-2 trial[3] have provided an accurate picture of the numbers and types of patients presenting on discharge from the hospital with either clinical heart failure or signs of severe left ventricular damage. This group is fairly large

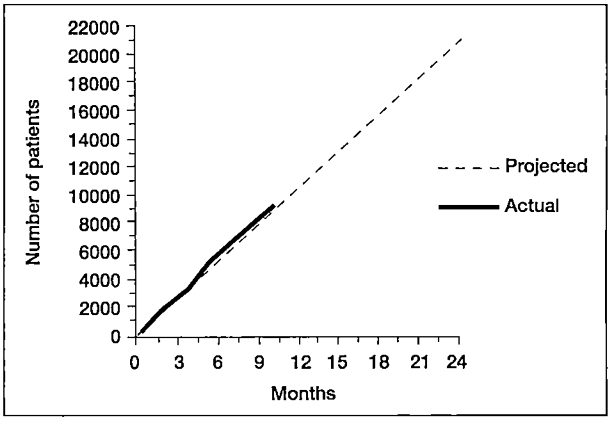

FIGURE 2. GISSI-3 recruitment.

(14%), has poor prospects in terms of quality of life, and has a high risk of mortality (9.8% in patients with signs or symptoms of severe left ventricular dysfunction vs 2.0% in the remaining population). Additional measures to limit ventricular damage are therefore essential to reduce morbidity and mortality further.

Experimental findings indicate the expansion of the infarcted area and left ventricular remodeling and dilation are early events in AMI, laying the bases for progressive dilation and dysfunction of the left ventricle.[7–10] Drugs acting on left ventricular load during and after AMI might prevent (or limit) the onset and progression of this process and have a favorable impact on the patients' clinical course, both by reducing mortality and by improving left ventricular function.[8] Although the efficacy of these drugs in improving left ventricular function in patients with heart failure has already been demonstrated, it is now important to assess whether a treatment started very early after AMI may also prevent the occurrence of left ventricular dysfunction beyond the period of active treatment.

In many respects nitrates and angiotensin-converting enzyme (ACE) inhibitors appear to be ideal candidates for a prevention strategy starting in the acute phase.

Nitrates: Clinical and experimental findings document the effect of nitrates in reduction of infarct size.[11] Clinical findings indicate a reduction of the postinfarct asynergic area, of the end-diastolic and end-systolic volumes, and an increase in the ejection fraction,[12] and meta-analysis of the results of randomized clinical trials suggests a significant reduction in mortality.[13] Nevertheless, a prospective controlled assessment of their efficacy is still lacking, for studies carried out so far are extremely heterogeneous with respect to timing of treatment and drug dosages employed, having been conducted in the 1970s on populations whose mortality rates are currently unrealistic and using therapeutic strategies no longer considered valid.

ACE inhibitors: Experimental findings document a reduction in postinfarct ventricular dilation and lower mortality rates in animals treated early and long term.[14,15] Pharmacologic data increasingly suggest a specific tissue role, with different and potentially complementary mechanisms, e.g., inhibition of cardiac myocyte hypertrophy or arterial myointimal proliferation.[16–18] Controlled clinical trials indicate that ACE inhibitors might prevent left ventricular dilation progression,[19,20] and the question of whether these drugs actually reduce mortality in the postdischarge phase of AMI has recently been explored in the Survival and Ventricular Enlargement (SAVE) study, the results of which were reported at the 41st American College of Cardiology Congress in Dallas in April 1992.

Combined treatment with nitrates and ACE inhibitors: An interaction in terms of efficacy and safety can reasonably be expected due to the different mechanisms of action of nitrates and ACE inhibitors. The frequent association of the 2 drug classes in routine clinical practice shows the need for further formal investigation of the interaction with a factorial study design.

Although the results of recent large-scale trials clearly show that all AMI patients can be expected to benefit from these treatments in terms of mortality and ventricular function, the same data also suggest the existence of important subgroups of patients with quite different prognostic experiences. The large number of events occurring in women and in patients >70 years of age calls for the separate assessment of treatment effects within these subpopulations.

AIMS OF GISSI-3 AND OUTCOME MEASURES

Primary aims are to evaluate the effects of a 6-week treatment course with ACE inhibitors and/or nitrates on early (6 weeks) and late (6 months) mortality following myocardial infarction, and to assess whether these treatments reduce the risk of left ventricular dysfunction to a clinically relevant extent, the benefit being deemed clinically relevant if still detectable 6 months after the infarction.

The choice of the main outcome measures and of their timing clearly reflects the objectives outlined above:

1. Mortality is assessed at 6 weeks and at 6 months, to evaluate the efficacy of treatments in the early phase following the AMI and over medium term, respectively.
2. As a measure of the overall efficacy of the treatments under study, a combined 6-month endpoint is also adopted, consisting of the sum of hard events (mortality and severe left ventricular dysfunction) occurring while on drug treatment and/or after withdrawal. Severe left ventricular dysfunction and mortality are both counted as "failures." If left ventricular dysfunction leads to death within the follow-up period, only the latter event will be considered.

Subsidiary aims are to assess treatment effects on the combined endpoint at 6 weeks, bearing in mind the confounding of symptomatic and structural effects while on therapy, to evaluate potential positive or negative interactions of ACE inhibitors and nitrates and their effect on mortality and severe left ventricular dysfunction, and to assess treatment effects in patients with and without thrombolysis. The safety profile of ACE inhibitors and nitrates administered separately and in combination will also be studied.

Specific studies: Three separate evaluations will be conducted on subpopulations:

1. assessment of treatment effects in women and in patients >70 years old;
2. evaluation of treatment effects on the instrumental evidence of progression of left ventricular dilation;
3. comparison of treatments with respect to quality of health.

GENERAL OUTLINE OF THE STUDY

The experimental study design (Figure 3) has a 2 × 2 factorial structure with 4 treatment groups: lisinopril alone, nitrates alone, combined therapy, and no trial therapy. The study is randomized and open.

Treatments assigned by randomization are withdrawn at 6 weeks, at which time mortality is assessed. Patients are followed up to 6 months for the evaluation of both mortality and combined endpoint.

Routine treatments: In addition to the drug assigned by randomization, patients are treated according to the participating coronary care unit's routine clinical practice, and with thrombolytics, intravenous β blockers, and aspirin as soon as possible after admission, in the absence of specific contraindications. Patients are given any treatment clearly required by their clinical conditions at any time, including (if needed) any of the drugs under study, irrespective of the allocated regimen. Conditions such as heart failure, hypertension or angina can contraindicate discontinuation of the trial treatments at 6 weeks, or suggest the opportunity of instituting treatment with any of the drugs under study.

Subjects with persistent angina, hypertension, or heart failure randomly assigned to lisinopril or to the control group are given nitrates until the clinical situation becomes stable.

Risk stratification: Patients are evaluated by their coronary care units at discharge, according to the scheme applied in GISSI-2, which represents a standard of good clinical practice (exercise test, echocardiogram, 24-hour Holter monitoring).

Ascertainment of the events included in the combined endpoint: The combined endpoint includes death and late clinical congestive heart failure (beyond day 4 of hospital stay), or extensive left ventricular damage in the absence of clinical heart failure. Late clinical congestive heart failure diagnosis is based on the presence of at least 2 of the following signs or symptoms: bibasilar pulmonary rales, third heart sound, dyspnea, and radiographic evidence of pulmonary congestion. Extensive left ventricular damage, not clinically evident, is identified by observation of a left ventricular ejection fraction ≤35%, or ≥45% myocardial segments injured as indicated by 2-dimensional echocardiography.[21]

STUDY POPULATION AND OPERATIVE PROCEDURES

Admission criteria: All patients admitted to the hospital within 24 hours of the onset of symptoms with a diagnosis of AMI based on clinical and laboratory criteria will be enrolled, irrespective of their eligibility for thrombolytic treatment.

The diagnostic criteria adopted include pain of typical intensity and duration and echocardio-

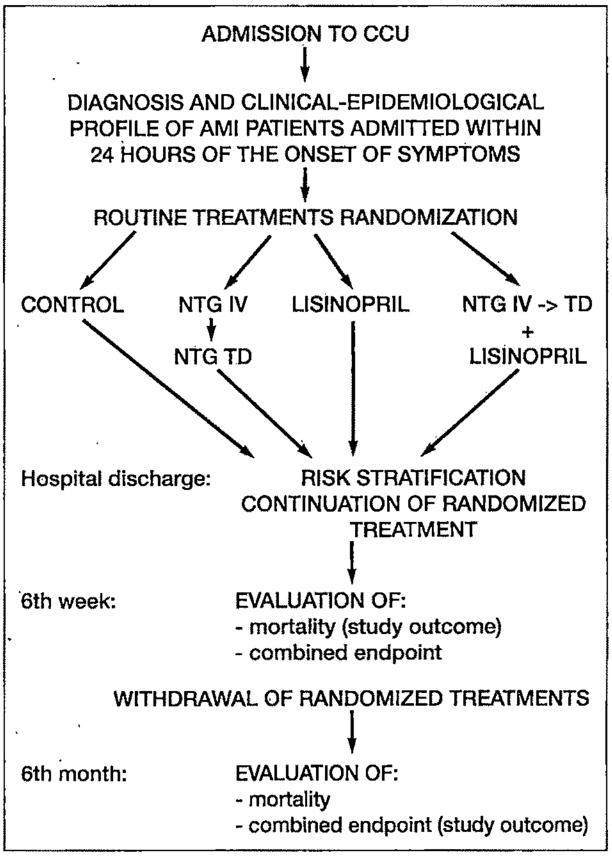
ADMISSION TO CCU
DIAGNOSIS AND CLINICAL-EPIDEMIOLOGICAL PROFILE OF AMI PATIENTS ADMITTED WITHIN 24 HOURS OF THE ONSET OF SYMPTOMS
ROUTINE TREATMENTS RANDOMIZATION
CONTROL
NTG IV
NTG TD
LISINOPRIL
NTG IV -> TD
+
LISINOPRIL
Hospital discharge:
RISK STRATIFICATION
CONTINUATION OF RANDOMIZED TREATMENT
6th week:
EVALUATION OF:
- mortality (study outcome)
- combined endpoint
WITHDRAWAL OF RANDOMIZED TREATMENTS
6th month:
EVALUATION OF:
- mortality
- combined endpoint (study outcome)

FIGURE 3. Study design. AMI = acute myocardial infarction; CCU = coronary care unit; NTG IV = intravenous nitroglycerin; NTG TD = transdermal nitroglycerin.

graphic changes (up- or down-sloping of the ST segment of ≥1 mm in ≥1 peripheral leads, or of ≥2 mm in ≥1 precordial leads). Due to the broadening of the time window for entry, ST changes might partially or completely attenuate; if so, a history of typical pain accompanied by a critical increase of creatine phosphokinase to at least twice the upper threshold of the normal range is sufficient diagnostic criterion for entry into the study.

Exclusion criteria: Patients are ineligible for randomization if any of the following conditions are present: (1) severe heart failure requiring any of the study treatments; (2) high risk of further serious hemodynamic deterioration if vasodilators are used (systolic blood pressure ≤100 mm Hg, Killip class 4). The contraindication for hypotension is valid as long as the condition persists; the patient may be randomized if systolic blood pressure increases to >100 mm Hg during the 24 hours following the onset of symptoms, provided that no other contraindications are present; (3) similarly, marked clinical and/or hemodynamic instability (e.g., persistent angina, hypotension) might temporarily contraindicate treatment with the study drugs; however, if stable conditions are reached within the first 24 hours, the patient can be reevaluated for randomization. Special care is recommended for patients presenting with right ventricular infarction and/or right ventricular failure (since the study drugs might worsen their hemodynamic condition), or definite diagnosis of glaucoma at entry. The decision on whether these patients should be randomized or not is left entirely to the discretion of the attending physician; (4) specific contraindications to the use of the drugs under trial, namely, a history of clinically relevant renal failure (creatinine >2 mg/24 hours and/or proteinuria >500 mg/24 hours), or of bilateral stenosis of the renal arteries, or a documented allergy to 1 of the drugs under study; (5) life-threatening conditions in the short term, other than AMI (such as tumors, serious respiratory diseases, etc.); and (6) prior randomization within the trial.

Randomization procedure: Eligible patients are randomized as soon as possible after diagnostic confirmation. Randomization will be done on a 24-hour basis, 7 days a week, by a telephone call to the randomization service.

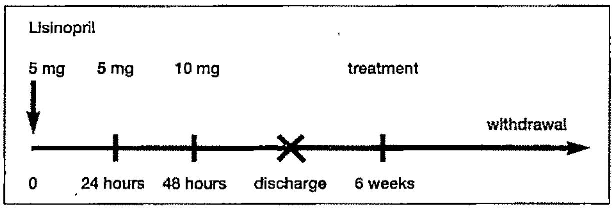

FIGURE 4. Treatment schedule for administration of oral lisinopril.

Administration of active treatment: Immediately after randomization, patients receive the allocated drug(s). Patients allocated to ACE inhibitors receive lisinopril orally. Those patients assigned to nitrates receive nitroglycerin intravenously during the first 24 hours following AMI, and subsequently via a transdermal patch applied during the day, so as to allow a 10-hour treatment-free interval intended to minimize development of tolerance to nitrates and the resulting response reduction.

Treatment schedules: NITRATES: Nitroglycerin is administered during the first 24 hours by intravenous infusion at a starting rate of 5 mg/min, increased by 5–20 mg/min every 5 minutes for the first 30 minutes until systolic blood pressure has decreased at least 10%, provided it remains above 90 mm Hg. At 24 hours after AMI, the intravenous nitrate is replaced with a transdermal formulation providing 10 mg nitroglycerin (Deponit, Schwarz-Pharma). If the patch is not tolerated by the patient or its adhesion to the skin is not satisfactory, a single oral dose of 50 mg isosorbide-5-mononitrate capsules (Elan Retard, Schwarz-Pharma) is given daily. This preparation should be as effective as the transdermal formulation in minimizing the development of tolerance. If patients complain of persistent headache, hypotension, palpitations, tachycardia, or dizziness, the transdermal preparation will be switched temporarily to the 5 mg formulation, and those on oral isosorbide are treated with 20 mg doses twice daily.

ACE INHIBITORS: Lisinopril (Zestril, ICI Pharma) is administered orally according to the schedule shown in Figure 4. Since the pilot study showed a higher risk of persistent hypotension among patients with systolic blood pressure ≤120 mm Hg at randomization or in the first 3 days, these subjects are treated with a lower dose (2.5 mg).

A lisinopril maintenance dose of 5 mg will be adopted in cases of hypotension (systolic blood pressure ≤100 mm Hg) occurring at any time during the study and temporary reductions to 2.5 mg are allowed. The minimum maintenance dose of lisinopril is 5 mg/day, and if severe hypotension (systolic blood pressure ≤90 mm Hg) persists, lisinopril is to be stopped. Patients randomly assigned to lisinopril who have persistent angina, hypertension, or heart failure are given nitrates until the clinical situation stabilizes.

If study treatments are temporarily withheld during the first 6 weeks (when clinical conditions strongly indicate this course of action), they are to be reinstituted as soon as possible.

Follow-up of AMI survivors: The 6-week and 6-month follow-up visits include clinical examination and bidimensional echocardiogram. The bidimensional echocardiogram at 6 weeks is performed >24 hours after drug withdrawal.

AMI patients not randomized: A registry of all patients admitted to the coronary care unit within 24 hours from onset of symptoms and not entered into the trial is being kept, recording the reasons for nonrandomization.

Reporting of adverse drug events: To fulfill regulatory authority requirements, serious and unexpected adverse events thought to be related to trial treatment should be reported within 3 working days by the responsible physician to the Scientific and Organizing Secretariat.

Serious adverse events are defined as fatal, life-threatening, or disabling events thought to be due to trial treatments. Unexpected adverse events are all events not commonly expected among patients with a diagnosis of acute myocardial infarction (expected events being death, reinfarction, arrhythmias, cardiac rupture, heart failure, cardiogenic shock, etc.).

Standard reporting procedures: The Scientific and Organizing Secretariat is responsible for the practical study management, namely, for collection, quality control, and computerized handling of data. The standard operating procedures for data collection and control as submitted to the U.S. Food and Drug Administration are as follows.

Each center identifies a clinical monitor (a junior cardiologist working full-time in the coronary care unit, who receives ad hoc financial support from the study), who is specifically trained for data collection procedures. He is responsible for the completion and checking of the forms of the center as well as for ensuring that copies of the original documentation required to confirm clinical events and death reach the Scientific Secretariat.

On completion, the original copy of the study form (which includes all predefined information up to the 6 weeks foreseen for the evaluation of the cumulative endpoint) is mailed in a preaddressed and prepaid envelope to the Scientific Secretariat. A computer generated alert (based on the date of randomization) is issued 15, 30, and 45 days after the 6-week period of each patient elapsed, to monitor the timely arrival of forms and to trace closely those that are delayed.

On arrival, each form is filed after appropriate matching with the identification produced at the time of randomization, and it is checked for completeness and consistency of material data by a data monitor. A team of cardiologists review the forms qualitatively with respect to clinical information and items. Each inconsistency or lack of data requires an immediate contact with the center, through phone and/or fax, until doubts and controversies are cleared (visits to the centers are scheduled not only at periodic intervals, but every time the quality of the data is consistently below standard).

Validated documents are scheduled for standard computer-controlled data input by a dedicated team under the supervision of the Scientific and Organizing Secretariat. A quality control evaluation on a random sample of forms is to be conducted on 5% of all forms, and systematically for all data related to main endpoints and events.

Original medical records and forms related to predefined events (given on the main data collection sheet) and death are obtained from the hospital, and examined by an ad hoc "attribution committee" (composed of 3 senior clinicians) blind with respect to the assigned treatments.

After their use for data input, original forms are filed in hospital-dedicated folders and kept for control and inspection by health or regulatory public authorities.

A quality control program on the 10% of all instrumental results included in the cumulated endpoint has been organized with the same scheme that has proved to be highly successful in GISSI-2.

STUDY SIZE

Given the wide recruitment window adopted (up to 24 hours, patients receiving thrombolysis or not), it is reasonable to assume mortality and combined endpoint rates at least of a similar order of magnitude as in GISSI-2 (thrombolysed patients, within 6 hours).

Hence, the size of the study was determined on baseline rates of 10% and of 23% for mortality and for the combined endpoint, respectively.

A trial involving 20,000 patients allows the detection of a mortality rate reduction of at least 20% between main treatment arms (lisinopril vs no lisinopril and nitrates vs no nitrates), as well as of positive or negative interactions between treatments. A trial of this size also has a reasonable chance of detecting a 20% difference in main outcomes within the separate subpopulations of females and of elderly patients. About 4,000 women and 4,500 subjects >70 years old are likely to be entered into the study, with baseline combined endpoint rates of 30% and 40%, respectively.

Expected patient numbers for assessment of mortality: Comparison will be made between randomized treatments and controls: no nitrates (10,000 patients) vs nitrates (10,000 patients); no lisinopril (10,000 patients) vs lisinopril (10,000 patients); expected mortality of 10% (1,000 patients) with a 20% reduction to an expected mortality of 8% (800 patients; alpha <0.01; 1-beta <0.95, 2-sided).

Comparison will be also made between lisinopril plus nitrates and controls: controls (5,000 patients) vs lisinopril plus nitrates(5,000 patients); expected events = 10% (500 patients) with a 30% reduction to expected events = 7% (350 patients; alpha <0.01; 1-beta <0.95, 2-sided).

Expected patient numbers for assessment of the combined endpoint: Comparison will be made between randomized treatment and controls:no nitrates (10,000 patients) vs nitrates (10,000 patients); no lisinopril (10,000 patients) vs lisinopril (10,000 patients); expected events = 23% (2,300 patients) with a 20% reduction to expected events = 18.4% (1,840 patients; alpha <0.01; 1-beta <0.95, 2-sided).

Comparison will be also made between individual active treatments and controls: controls (5,000 patients) vs nitrates alone (5,000 patients); controls (5,000 patients) vs lisinopril alone (5,000 patients); expected events = 23% (1,150 patients) with a 20% reduction to expected events = 18.4% (920 patients; alpha <0.1; 1-beta <0.95, 2-sided).

Comparison will be made between randomized treatments: first active treatment (5,000 patients) vs second active treatment (5,000 patients); expected events = 18.4% (920 patients) with a 15% reduction to expected events = 15.6% (782 patients; alpha <0.01; 1-beta <0.80, 2-sided).

Comparison will be also made between lisinopril plus nitrates and controls: controls (5,000 patients) vs lisinopril plus nitrates (5,000 patients); expected events = 23% (1,150 patients) with a 30% reduction to expected events = 16.1% (805 patients; alpha <0.1; 1-beta <0.95, 2-sided).

INFORMED CONSENT

The philosophy adopted in this respect is the same as that of the earlier GISSI trials, i.e., it is considered unethical to load the patient with the responsibility of expressing consent while in the hyperacute phase of a severe event such as an AMI.

When this phase is over, the patient will be clearly informed about participation in a randomized clinical trial. The patient's consent to continue randomized treatment will preferably be obtained in writing. Verbal consent will be documented in the patient's clinical records and signed by the attending physician and a witness (e.g., a nurse).

The consent form and the wording of the text to be read to the patients if verbal consent is sought have been approved by the Ethical Committee.

DATA MONITORING

The committees listed in the Appendix are responsible for the scientific management of the study.

The Safety and Data Monitoring Committee has blinded access to all study data and is specifically charged with monitoring informed consent procedures and the safety and efficacy profile of trial treatments.

The main analyses will be conducted by intention to treat; outcome differences, however, shall also be assessed by treatments actually received so as to evaluate the extent to which they might be due to different cointervention strategies. Safety analyses will be submitted to the Safety and Data Monitoring Committee after 1,000, 3,000, and 6,000 consecutive patients have completed 6 weeks' follow-up. Because of the expected timetable of recruitment, no formal interim analysis or stopping rules for efficacy are foreseen. The accrual of consecutive patients to numbers useful for reliable statistical assessment on the main endpoint at 6 months will coincide with the end of the randomization period.

APPENDIX

The following Committees are responsible for the scientific management of the study.

Steering Committee: C. De Vita, E. Geraci, L. Tavazzi, G. Tognoni, C. Vecchio (Chairman). **Safety and Data Monitoring Committee:** R. Boeri, G.D. D'Amico, U. Loi, E. Marubini, L. Pagliaro, F. Rovelli (Chairman). **Scientific and Organizing Secretariat:** M.G. Franzosi, A.P. Maggioni, F. Mauri, A. Volpi. **Data Management and Analysis:** E. Santoro, E. Negri. **Clinical Data and Echocardiographic Data Revision:** E. Bonfanti, A. Nobili, L. Staszewsky, D. Torta, G. Ventura. **Scientific Committee for Side Projects:** M. Disertori, P.F. Fazzini, S. Garattini, P. Marino, A. Maseri, G. Mazzotta, G. Nicolosi, S. Pirelli, G. Sanna, F. Valagussa, N.

Braggio (Observer), S. Frezzati (Observer). **International Advisory Board:** S. Yusuf, R. Peto, S. Pocock, H.J. Dargie.

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Long-Acting Angiotensin-Converting Enzyme Inhibition: Once-Daily Lisinopril Versus Twice-Daily Captopril in Mild-to-Moderate Heart Failure

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Once-daily lisinopril (5–20 mg) was compared with twice-daily captopril (12.5–50 mg) in a double-blind, randomized, parallel-group study of angiotensin-converting enzyme (ACE) inhibition conducted in 31 centers for 12 weeks in patients with heart failure (New York Heart Association class II–III) who were currently receiving digitalis and/or diuretics. The drugs were compared with regard to their effects on exercise duration, measured with bicycle ergometry, and on ectopic activity, measured using Holter monitoring. Both drugs significantly increased exercise duration after both 6 and 12 weeks of randomized treatment. Neither ACE inhibitor had any significant impact on the hourly rate of either ventricular ectopic counts or couplets, nor was there any difference between treatments with regard to the proportions of patients in whom ventricular ectopic counts were reduced. Both drugs were well tolerated, with no differences observed between treatments. Potassium, urea, and creatinine levels remained stable for both treatments throughout the study.

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Following the recent publication of several major studies on the use of inhibitors of angiotensin-converting enzyme (ACE), the use of these drugs in the treatment of moderate and severe congestive heart failure (CHF; New York Heart Association [NYHA] classes III and IV) has now become standard practice as an addition to the use of diuretic drugs and/or digitalis.[1] This relatively new class of agents is beginning to replace the use of other vasodilators, especially as they have been shown to have superior efficacy over some of the older vasodilator therapies.[2] Despite the wide acceptance of ACE inhibitors in the treatment of CHF, there remains some debate as to the relative merits of short-acting and long-acting drugs of this class.[3,4] Packer et al[3] have demonstrated that under certain conditions, relative hypotension and renal impairment were more frequently found in patients treated with a long-acting ACE inhibitor, enalapril, than in those patients treated with a short-acting ACE inhibitor, captopril. Conversely, Giles et al[4] demonstrated that once-daily lisinopril is at least as effective as 3 times daily captopril when these drugs are coadministered with digitalis and/or diuretics in patients with NYHA classes II–IV heart failure. Additionally, this study demonstrated that the administration of a long-acting ACE inhibitor once daily was not associated with a significantly greater risk of adverse events.

The primary aim of the study reported here was to compare the efficacy of once-daily lisinopril with twice-daily captopril in the treatment of patients with mild-to-moderate heart failure (NYHA classes II and III), maintained on optimal doses of digitalis and/or diuretics. In addition, an investigation of the effect of these ACE inhibitors on ventricular ectopic activity, as measured by 24-hour electrocardiographic Holter monitoring, was undertaken.

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METHODS

Patients: Male or female patients >21 years old with the clinical signs and symptoms of CHF (NYHA classes II and III), were considered eligible for entry into the study. The diagnosis of CHF was confirmed by the use of chest radiograph (cardiothoracic ratio >0.5), radioisotope scan, or echocardiography (ejection fraction <45%). All patients had to be capable of performing an exercise protocol for 4–12 minutes on a bicycle ergometer. All were symptomatic on stable doses of either digitalis or diuretics or both. Patients were excluded from the study if they had a recent history of myocardial infarction or cardiac surgery (including percutaneous transluminal coronary angioplasty), cerebrovascular accident, clinically important renal disorders, or right heart failure. Patients with intrinsic lung disease limiting exercise performance were also excluded, as were those with arrhythmias that required therapy, other than with digoxin or amiodarone. Women capable of childbearing and patients with fixed rate cardiac pacemakers were also excluded. Patients with a history of liver, blood, or endocrine disorders or clinically significant abnormal levels of serum potassium were not permitted to enter the study, as were those with any known hypersensitivities or other contraindications to ACE inhibitors. Patients with a known history of drug or alcohol abuse were also excluded, and in some centers patients who had reduced absorption following gastrointestinal surgery or those who had taken part recently in another medical study were also excluded. Patients were informed of the aims, methods, possible benefits, and hazards of the study, and gave their informed consent to enter into the study. This study was conducted in accordance with the Declaration of Helsinki (revised Venice 1983), and local ethics committee approval was obtained.

Study design: The study was a double-blind, parallel-group, randomized, multicenter design. The study incorporated a placebo baseline period of 10–14 days, during which time the digoxin and/or diuretic doses were optimized according to the patients' symptoms, and all other vasodilator and ACE inhibitor therapies were withdrawn. Patients were then randomized to either lisinopril or captopril for 12 weeks. The randomization was carried out using a separate randomization scheme, which was generated for each participating center. At the end of the baseline period, patients were assigned to a treatment group, using the computer-generated random scheme for that center. During the run-in period, placebo tablets (matching 2.5 mg lisinopril taken once daily, and matching 12.5 mg captopril taken twice daily) were administered to the patients single blind. The initial dose of the double-blind treatment was given as a single oral dose of either 2.5 mg lisinopril or 6.25 mg captopril. Any symptoms reported or experienced by the patient were fully documented.

To achieve double-blind treatment during the active treatment period, a double-dummy technique was employed. On each day patients who received lisinopril also took the appropriate number of placebo tablets matching captopril tablets and vice versa. In the case of patients randomized to lisinopril, after monitoring the effect of the initial dose (2.5 mg), 1 lisinopril tablet (5 mg) was taken per day. If, after 2 weeks of this treatment, there was evidence of clinical improvement, then the patient continued on that dosage thereafter. An increase in the dose of study medication was considered after 2 weeks of randomized treatment, and again after a further 2 weeks of randomized treatment if the following 2 safety conditions were met: (1) standing systolic blood pressure was ≥90 mm Hg, and (2) there were no symptoms of hypotension (syncope, faintness, orthostatic dizziness) on the current dose and there was evidence of a need for additional therapeutic effect in the opinion of the investigators. If the dosage of study medication needed to be increased after 2 weeks, lisinopril dosage was increased to 10 mg once daily and, again, after a further 2 weeks of treatment lisinopril could be increased to a maximum of 20 mg once daily. The dose of lisinopril was reduced at any relevant visit if (in the view of the investigator) the patient was exhibiting symptomatic hypotension or any other adverse event.

For patients who received captopril, 1 captopril tablet (12.5 mg) was taken twice daily after monitoring the effect of the initial dose (6.25 mg). If after 2 weeks' randomized treatment there was evidence of clinical improvement, then the patient continued on a dosage of captopril 12.5 mg twice daily thereafter. An increase in the dose of the study medication to 25 mg twice daily was considered after 2 weeks of randomized treatment if the previous safety conditions and the need for further efficacy were met. If after a further 2 weeks of treatment the dosage of study medication needed to be increased, captopril doses were increased to a maximum of 50 mg twice daily. As was the case for the lisinopril-treated group of patients, the dosage of captopril could also be reduced at the discretion of the investigator if the symptoms so indicated.

Concurrent medication: Patients taking digitalis were to be maintained on a constant dose throughout the study. If evidence of toxicity appeared, the dose was either reduced or treatment discontinued. The morning dose of diuretic was withheld on the day the patient received the initial dose of randomized treatment. Thereafter, the diuretic dose was adjusted during the randomized-treatment phase as needed, based on the clinical assessment. Potassium-sparing diuretics were prohibited during the study. Serum potassium was anticipated to remain unchanged on ACE inhibitor treatment, or to increase slightly during the course of the study. However, if a patient developed hypokalemia, potassium supplements were administered. Additionally, sublingual nitroglycerin was taken as required. Chronic nitrate therapy, when used, was kept constant throughout the study. Concurrent therapy with anticoagulants was permitted; no other drugs known to affect preload or afterload could be administered during the course of this study.

Clinical assessment: A thorough physical examination of each patient was conducted at the time of entry into the study. An abbreviated symptom review and physical examination was performed at randomization, and this was repeated at the end of 12 weeks of randomized treatment.

Exercise testing was performed using an electrically braked bicycle ergometer and followed a schedule with continuous incremental workloads. All patients underwent a bicycle exercise test on 2 separate occasions during the placebo run-in, prior to entry into the randomized treatment phase of the study. The first exercise test served as a familiarization procedure for the patient, the second exercise test enabled the duration of exercise to be determined. Exercise tests were also carried out after 6 and 12 weeks of treatment. Patients undertook each exercise test at the same time of day (preferably in the morning), and medication was delayed on the day of the exercise test until measurements were complete.

Blood pressure was measured at each clinical visit on the same arm using a mercury sphygmomanometer. Heart rate was measured on each visit by palpation of the radial pulse over a 30-second period. Recordings of blood pressure and heart rate were made after the patient had been standing for 2 minutes. Classification of the patient according to the NYHA criteria was done by the same observer throughout the study and it was assessed at the end of the placebo run-in and after 12 weeks of treatment.

Holter monitoring was performed for a 24-hour period during placebo run-in and during the last week of treatment. The 24-hour electrocardiographic recordings were made using a 2-channel Holter monitor. Analysis of all 24-hour tapes was performed electronically by Hertford Medical (Hertford, UK).

Blood samples were obtained on entry to the study and after 12 weeks of treatment for hematology and biochemistry assessments, and at weeks 2, 4, and 6 of randomized treatment, for biochemistry assessment only. Full blood count and assessment of plasma urea, sodium, potassium, and creatinine were carried out.

Volunteered adverse events were obtained at each visit after the start of the placebo run-in period. In response to the question, "Have you had any symptoms or problems since your last visit?" the nature of any symptoms were recorded. Patients were asked to bring any unused tablets with them at each visit to assess compliance.

Statistical analysis: Statistical analysis was directed at estimating differences between the effects of lisinopril and captopril on exercise capacity after 12 weeks of therapy. Analysis of covariance was used to compare lisinopril and captopril for the change in exercise duration from the run-in visit to treatment week 6 and the change from the run-in visit to treatment week 12. The initial analysis of covariance took account of the following sources of variation: center, covariate, treatment, and center-by-treatment interaction. The exercise duration at the run-in visit was used as the covariate.

The influence of any patients withdrawing from the study or violating the protocol was investigated and the data used in the most appropriate manner to minimize bias. Previously published studies give an estimate of the variability of exercise duration data from bicycle exercise tests[5–7] and indicate a between-patient standard deviation from 1.4–3.1 minutes. To detect a minimum difference of 60 seconds in exercise duration between the 2 treatment groups, it was calculated that 172 patients (86 per group) would be required. This calculation assumed a 5% level of significance with 90% power, and assumed a standard deviation of 120 seconds. To allow for withdrawals it was planned that 250 patients (125 per group) were required for this study. Three analyses of exercise duration were carried out: *completers analysis, per protocol analysis,* and *last value analysis*. Of these analyses, the *completers analysis* assessed the treatment effects, ignoring potential bias or loss of precision due to withdrawals (13% of patients in this study) and protocol violators and deviators. In this regard, it is close to an analysis based on the "intention to treat" principle. The *per protocol analysis* fulfilled the study objectives with respect to the protocol. The *last value analysis* attempted to take account of the withdrawals in estimating the treatment effects. In this article, the results of the *completers analysis* are reported because the results and conclusions were the same as those obtained from the *per protocol analysis*.

Data on arrhythmias tend to have high variability, and the extent to which any treatment may reduce the incidence of arrhythmias is uncertain as is the clinical importance of any given reduction in CHF. Before any analysis could be undertaken, it was necessary to adjust the raw data recorded, because the individual periods of electrocardiographic monitoring were not exactly 24 hours and in many cases were much less than 24 hours. To allow for variations in the duration of electrocardiogram recording between different centers, the electrocardiographic data were converted to hourly rate for each recording, by dividing the values observed for the entire monitoring period by the duration of monitoring (hours). Only data from patients with a minimum of 8 hours of recording for both run-in and end of treatment assessment were summarized. Data from patients failing to satisfy this criterion were excluded from analyses of the electrocardiogram. In this report the results of the analysis based on patients completing the study alone are described, because the results and conclusions are the same as those obtained from a *per protocol analysis*. The skewed nature of the ventricular ectopic counts, couplet, and nonsustained ventricular tachycardia data suggested that it would be inappropriate to perform statistical analyses using parametric analysis of variance or covariance. These data were, therefore, analyzed using the nonparametric Wilcoxon rank-sum test. The proportion of patients in each treatment group with a reduction in the hourly rate of ventricular ectopic counts from run-in to week 12 was compared using Fisher's exact test.

The treatment effect was also assessed by summarizing the proportion of patients in each treatment group at week 12 whose ventricular ectopic activity was reduced. Two analyses of ventricular ectopic count, couplets and nonsustained ventricular tachycardia were carried out: *completers analysis* and *per protocol analysis*, based on the principles outlined above.

All safety data collected during the course of the study were collated and the proportion of patients who reported adverse events and those who withdrew due to adverse events, were compared for both lisinopril and captopril treatments, using Fisher's exact test. Because these analyses were concerned with treatment safety, data from all randomized patients were included.

TABLE I Demographic Variables for the Patients Randomized to Lisinopril or Captopril

Variable	Lisinopril	Captopril
Number patients	148	139
Males (%)	117 (79)	108 (78)
Females (%)	31 (21)	31 (22)
Mean age (yr)	59	59
Age range (yr)	29–83	33–82
Body weight (kg)	77.2	74.5
Etiology of heart failure* (%)		
Ischemic heart disease	52	49
Cardiomyopathy	35	41
Valvular heart disease	14	8
Hypertension	22	18
Other	9	5

*Some patients had more than 1 contributory factor for heart failure.

RESULTS

A total of 315 patients entered the study; 28 of these withdrew during the placebo run-in period and 38 withdrew during the randomized treatment period. The demographic details of the patients randomized to treatment with lisinopril or captopril are given in Table I, which shows that both groups of patients were well matched with respect to demographic variables. At the end of the study, 43% of captopril patients were receiving 25 mg daily, 34% received 50 mg daily, and 23% were taking 100 mg daily. In the lisinopril-treated group the 5, 10, and 20 mg daily doses were being taken by 44, 38, and 18% of the patients, respectively.

The effects of lisinopril and captopril treatment on exercise duration for weeks 6 and 12 of randomized treatment are shown in Figure 1. At 6 weeks, the exercise duration was increased with both treatments. The increase was slightly greater for lisinopril than for captopril. However, this relatively small difference (3 seconds) was not statistically significant. Exercise duration increased by 47.2 seconds on lisinopril and 44.3 seconds on captopril ($p = 0.77$). Similarly, after 12 weeks of randomized treatment, exercise duration was increased by both lisinopril and by captopril. The increase seen at week 12 was slightly greater for lisinopril than for captopril, but the difference (5 seconds) was not statistically significant ($p = 0.68$). When compared with initial run-in values on placebo, both lisinopril and captopril treatment in-

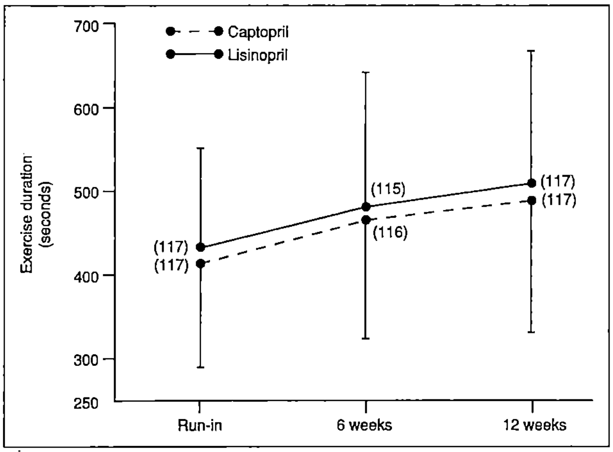

FIGURE 1. The effect of lisinopril and captopril on exercise capacity at the end of the run-in period and after 6 and 12 weeks of treatment. Numbers in parentheses indicate the number of patients in each group.

creased exercise duration at both 6 and 12 weeks significantly (p = 0.0001) in all cases.

24-hour electrocardiographic monitoring: There was no statistically significant difference between the treatments for the rates of ventricular ectopic counts or couplets. The median hourly rate for ventricular tachycardia was 0. Of 90 patients who received lisinopril, 51 (57%) and 50 of 93 patients (54%) who received captopril demonstrated a reduction in the hourly rate of ventricular ectopic counts from placebo run-in to the week 12 assessment. No significant difference between the 2 treatment groups was detected (p = 0.77).

Symptom review and physical examination: Figure 2 shows the percentage of randomized patients presenting with a particular symptom of heart failure both at placebo run-in assessment and after 12 weeks of randomized treatment. There was an overall improvement in the monitored symptoms following treatment for both groups of patients. With regard to the percentage of patients improving, the effect of treatment was similar for both captopril and lisinopril. Mean standing blood pressures and heart rate recorded at each visit remained consistent throughout the study in both treatment groups. No effects of treatment on the mean blood pressures or heart rate were observed.

Evaluation of NYHA class: Of the 125 lisinopril patients completing the study, 44 (35%) showed an improvement in NYHA status, 79 (63%) presented no change, and only 2 (1.6%) showed a deterioration in their condition. Of the 127 captopril patients completing the study, 51 (40%) showed improvement in their condition compared with 74 (58%) who showed no change and 2 (1.6%) who deteriorated (Figure 3).

Adverse events: Adverse events were reported for 23 of 148 patients (16%) who received lisinopril, and 21 of 139 patients (15%) who received captopril. No significant difference in the incidence of adverse events was seen between the 2 active treatment groups. Nine of 148 patients (6%) who were randomized to lisinopril and 7 of 139 patients (5%) who were randomized to captopril withdrew from the study due to adverse events (including death). The reasons for withdrawal are shown in Table II. There were no significant differences detected between the captopril and lisinopril treatment groups. Five patients treated with lisinopril

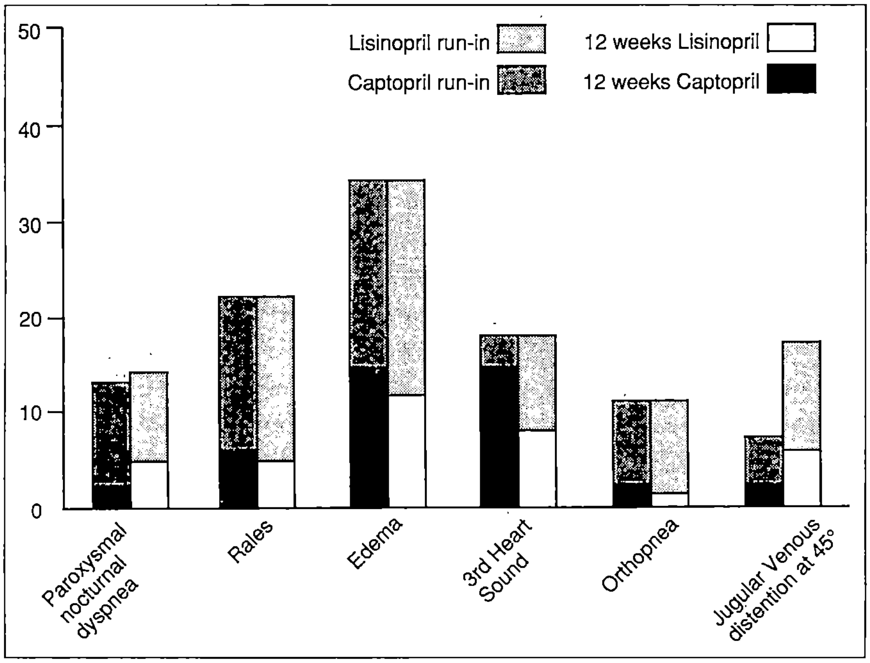

FIGURE 2. Percentage of patients with symptoms of heart failure present at run-in and after 12 weeks of treatment with either lisinopril or captopril.

and 2 patients treated with captopril died during the randomized phase of the trial. The causes of death in lisinopril-treated patients were pulmonary edema, ventricular fibrillation, sudden death (n = 2), and an accident. The 2 deaths on captopril treatment were due to cardiac failure following acute myocardial infarction and pulmonary edema. None of these deaths was considered to be related to treatment with the ACE inhibitors. Three patients died during the prerandomization phase of this study due to ventricular fibrillation (n = 1) and sudden death (n = 2). A total of 15 of 148 patients (10%) who received lisinopril and 15 of 139 patients (11%) who received captopril experienced adverse events that did not lead to withdrawal from the study.

No obvious treatment-related effects were observed in the laboratory parameters for either the lisinopril- or captopril-treated groups. Further, individual patient data showed no apparent treatment-related effects from either of these 2 drugs. Two patients who were treated with lisinopril showed changes in neutrophil count. For 1 of these patients, this value was above the laboratory normal range at entry and fell below the laboratory normal range after 12 weeks of treatment with lisinopril. The second patient displayed a decrease in neutrophil count but the value remained within the normal range throughout the study.

Mean plasma potassium concentration was unchanged after 12 weeks of treatment with captopril, 4.33 ± 0.44 mEq/liter at entry, compared with 4.35 ± 0.49 mEq/liter after 12 weeks. In contrast, the mean plasma potassium concentration increased on lisinopril treatment from 4.30 ± 0.43 mEq/liter at entry to 4.38 ± 0.39 mEq/liter at the end of 12 weeks of treatment. Per patient, 39% of captopril-treated patients and 36% of lisinopril-treated patients showed a decrease in plasma potassium of > 0.5 mEq/liter and 53% of captopril and 56% of lisinopril patients showed an increase of plasma potassium > 0.5 mEq/liter. These changes, however, were not significant, and there were no differences between treatments.

TABLE II Adverse Events Including Death Leading to Withdrawal of Treatment*

	Lisinopril	Captopril
Deaths	Pulmonary edema	Pulmonary edema
	Accident	Cardiac failure due to acute myocardial infarction
	Ventricular fibrillation	
	Sudden death (2 patients)	
Other events	Abdominal pain	Prurigo
	Tingling sensation	Exanthema
	Headaches	Vertigo
	Myocardial infarction	Feeling unwell
	Coughing	Headaches
	Dyspnea	Taste unusual
	Blood urea nitrogen increased	Coughing
	Hyperkalemia	Dizziness

*Some patients had more than 1 adverse event leading to withdrawal.

Plasma urea concentrations fell slightly, but not significantly, after lisinopril and captopril treatment. At entry the mean plasma urea concentrations were 6.42 ± 2.68 and 6.13 ± 2.69 mmol/liter for lisinopril and captopril, respectively. After 12 weeks of treatment the plasma urea concentrations were 6.32 ± 2.48 mmol/liter for lisinopril and 5.92 ± 2.35 mmol/liter for captopril. Of the captopril-treated patients, 11% showed a decrease in plasma urea concentrations greater than the predefined limit of 1.7 mmol/liter and an increase in

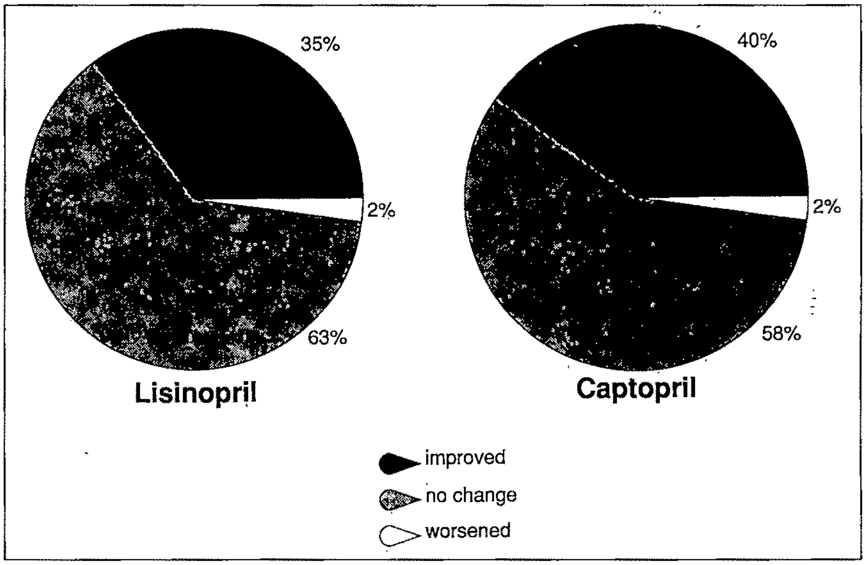

FIGURE 3. Change in functional status of patients completing 12 weeks of treatment, as assessed by New York Heart Association grading.

plasma urea concentration greater than 1.7 mmol/liter was seen in 13%. The corresponding figures for the lisinopril-treated group were 13% and 14%, respectively.

The mean plasma creatinine concentration was not significantly increased from 92.9 ± 19.2 μmol/liter at entry to 94.0 ± 20.4 μmol/liter after 12 weeks of treatment with lisinopril. Mean plasma creatinine concentration fell on captopril treatment from 93.1 ± 20.2 μmol/liter at entry to 93.0 ± 19.3 μmol/liter during 12 weeks of treatment. A decrease in plasma creatinine concentration greater than the predefined limit of 17.7 μmol/liter was seen in 10% of lisinopril- and 9% of captopril-treated patients and increases in plasma creatinine >26.5 μmol/liter were seen in 8% of both captopril- and lisinopril-treated patients.

Other routine biochemical analyses indicated no obvious treatment-related effects for either lisinopril- or captopril-treated groups. The individual patient biochemical data did not show any obvious treatment-related effects. No discernible differences between the treatment groups were seen.

DISCUSSION

This study demonstrates the equivalence of once-daily lisinopril and twice-daily captopril in patients with mild to moderate heart failure. Both treatments produced significant, but very similar, improvements in the exercise capacity of the patients. A previous study in which once-daily lisinopril was compared with 3 times daily captopril showed a greater improvement in exercise capacity in lisinopril-treated patients compared with the captopril-treated patients (using a *per protocol analysis*).[4] The results of this study appear to be at variance with this earlier work. However, there may be several reasons for the apparent lack of difference between the 2 treatments seen in this present study. This study employed bicycle ergometry to assess exercise capacity rather than a treadmill test. A previous study in which lisinopril was compared with placebo, and which used both treadmill and bicycle ergometry testing, produced different exercise times for these 2 methods with smaller differences between the ACE inhibitor and placebo for the bicycle ergometry.[8] However, larger differences have been observed in other placebo-controlled studies of lisinopril.[9] The shorter exercise times observed using bicycle ergometry may make any small differences between treatments more difficult to detect than by using the longer exercise times of the treadmill tests.

In the present study the time of assessment of exercise capacity in relation to the timing of the previous dose of medication was different from that reported in a previous comparative study.[4] In the latter study, exercise capacity was measured during the day at no particularly fixed relation to the timing of the last dose of the study medication. However, in the present study the exercise capacity was assessed at least 24 hours after the last lisinopril dose and at least 12 hours after the last captopril dose. Under the conditions of this study, it is anticipated that the blood (and tissue) levels of both drugs would be at their respective nadirs at the time of exercise assessment, perhaps minimizing any differences between the treatments that might have been observed had blood concentrations of the respective drugs been higher.

Packer,[10] has suggested that a fully effective study in heart failure may require treatment to be optimized to maximum levels and that a period of 3 months' treatment may then be required to eliminate any placebo effect and to demonstrate the full value of treatment. In the present study, the majority of patients were on the lowest effective dose of trial drug, and although the study was of 12 weeks' duration a portion of this time was taken up by a dose-titration phase. If Packer's[10] suggestions are correct, this study may have been too short and may have used doses too low to separate the effects of lisinopril and captopril completely satisfactorily.

It is noteworthy that, with regard to overall NYHA grading, in the present study the 2 treatments were indistinguishable, both achieving an improvement in status of ≥35%, suggesting that on a global rating, both drug treatments were equivalent.

Neither ACE inhibitor had any significant impact on the hourly rate of either ventricular ectopic counts or couplets, nor was there any difference between treatments with regard to the proportion of patients in which ventricular ectopic count rates were reduced. Despite the effect of both ACE inhibitor treatments on ventricular ectopic counts it is unlikely to be of clinical importance. In the earlier Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[11] enalapril treatment reduced mortality principally by reducing the frequency of deaths due to worsening heart failure rather than those attributed to sudden cardiac death. Considering the observations of the present study, and taken together with the finding of the CONSENSUS study,[11] the data suggest that, although ACE inhibitors will reduce the frequency of ventricular ectopic counts in a proportion of patients, this effect may be attributable primarily to their effects on the underlying pathologic condition causing the cardiac heart failure, rather than to a direct antiarrhythmic effect.

Both once-daily lisinopril and twice-daily captopril were equally well tolerated and any adverse events observed were in line with those previously observed in heart failure patients treated with ACE inhibitors. Cough was infrequently reported in both treatment groups. An adverse effect on renal function, reflecting the effect of treatment on systemic and renal hemodynamics, may occur during ACE inhibitor treatment in some patients with CHF.[12] In this regard, long-acting ACE inhibitors have been more frequently associated with increases in blood urea nitrogen and creatinine than have shorter-acting ACE inhibitors.[3] However, in the present study the values for plasma potassium, urea, and creatinine remained fairly steady throughout for both lisinopril and captopril treatments; indeed the use of lisinopril was not associated with an increased frequency of elevations in potassium, urea, or creatinine compared with captopril. Taken together, these observations indicate that administration of once-daily lisinopril was not associated with an increased risk of renal impairment compared with the shorter-acting captopril administered twice daily.

It is concluded that once-daily lisinopril 5–20 mg is as effective as twice-daily captopril 12.5–50 mg in terms of improvement of exercise capacity and changes in NYHA grading. Moreover, both drugs reduce the frequency of ventricular premature beats to an equal extent and are associated with a similar spectrum of adverse events in the heart failure patient.

APPENDIX

Members of the study group were as follows. **Germany:** Prof. A. Horsch (Speyer); Prof. D. Hey, Dr. K. Lindner (Bietigheim); Dr. P. Harbath, Dr. H.G. Gieretz (Bottrop); Dr. D. Storp, Dr. J. Heuse (Laatzen); Prof. P. Schuster (Eschweiler); Prof. J. Senges, Dr. M. Zander (Ludwigshafen); Dr. G. Pfeifer (Karlsruhe); Prof. J. Wagner, Dr. M. Pieper (Berlin); Prof. H.W. Hoepp, Dr. G. Mager, Dr. M. Hirsch (Köln); Prof. H. Simon, Dr. T. Ezzeldin (Düren); Prof. S. Gorlitz, Dr. R. Jacksch, Dr. A. Heidenblut (Essen); Prof. W. Kutscha, Dr. S. Roelcke (Landau); Dr. H.C. Hidajat (Rothenburg-Fulda); Dr. A. Kemmling (Völklingen); Dr. W. Mansury (Neuwied); Dr. L. Szappanos (Darmstadt); Dr. J. Heck, Dr. H.-P. Hobbach (Altenkirchen). **Italy:** Prof. A. Mancini, Dr. A. Ferrara, Prof. N. Mininni, Dr. G. De Simone, Dr. S. Severino, Prof. M. Cafiero, Dr. F. Benvenuto, Prof. O. De Divitiis, Dr. S. Di Somma (Naples); Prof. E. Correale, Dr. A. Brienza (Caserta); Prof. B. Ravera, Dr. A. Manaca (Salerno); Prof. L. Colonna, Dr. E. Fino (Bari); Prof. E. Geraci, Dr. F.P. Sabella (Palermo); Prof. R. Della Monica, Dr. A. Maliconico (Cara di Tirreui); Prof. F. Furlanello, Dr. G. Inama (Trento); Prof. G. Pinelli, Dr. G. Di Pasquale, Dr. A.M. Lusa, Dr. P. Grazi (Bologna); Prof. F. Rusticali, Dr. A. Catapano, Prof. C. Longhini, Dr. M. Vaccari, Dr. E. Baracca (Ferrara); Dr. L. Rossi, Dr. E. Carbonieri (Verona).

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Comparison of Treatment with Lisinopril Versus Enalapril for Congestive Heart Failure

Faiez Zannad, MD, Stan A.J. van den Broek, MD, and Michel Bory, MD

The effect of lisinopril 5–20 mg once daily or enalapril 5–20 mg once daily on exercise capacity, ventricular ectopic activity, and signs and symptoms of heart failure have been studied in 278 patients with mild-to-moderate (New York Heart Association [NYHA] classes II and III) heart failure in a randomized, double-blind, parallel-group study of 12 weeks' duration. Exercise duration was significantly increased by both angiotensin-converting enzyme (ACE) inhibitors after 6 and 12 weeks of treatment compared with their respective baseline values. There was a trend toward a greater increase in exercise duration on lisinopril after 12 weeks, although this did not reach statistical significance ($p = 0.0748$). There were no significant treatment differences with respect to the effect of the 2 drugs on ventricular ectopic counts, couplets, or nonsustained ventricular tachycardia. Both drugs were equally effective in improving NYHA grading and symptoms. Neither treatment had any significant effect on mean heart rate or mean blood pressures. Both treatments were equally well tolerated. The most commonly reported adverse events on both drugs were cough, dizziness, fall in blood pressure, vertigo, and myocardial infarction. The results of this study indicate that lisinopril 5–20 mg once daily is at least as effective and well tolerated as enalapril 5–20 mg once daily.

(Am J Cardiol 1992;70:78C–83C)

Angiotensin-converting enzyme (ACE) inhibitors are now considered to be a fundamental part of the treatment of congestive heart failure (CHF),[1] and in many respects individual drugs in this class are remarkably similar,[2] differing principally in their chemistry, metabolic fate, and duration of action.[3–5] Lisinopril is a relatively new ACE inhibitor that differs from captopril and enalapril in that it is neither a prodrug nor does it contain a sulfhydryl group.[3,6]

Previous studies of lisinopril in heart failure have shown it to have sustained hemodynamic effects[7] and it has proved to be effective in improving exercise capacity and signs and symptoms when used once daily compared with placebo.[8] Lisinopril has been compared once daily with captopril given 3 times daily,[9] and, on the basis of a *per protocol* analysis, lisinopril produced a greater improvement in exercise capacity than captopril.

Some studies have used enalapril once daily in the treatment of heart failure.[10–13] However, most have used the drug twice daily. Nevertheless, the pharmacokinetic half-life of enalapril (11.1 hours)[14] is consistent with use as a single daily dose, like lisinopril.[9,15] It was of interest, therefore, to compare the efficacy of lisinopril with that of enalapril when both treatments were given once daily to patients with mild-to-moderate CHF (New York Heart Association [NYHA] classes II and III). As a secondary objective, the effect of ACE inhibition with these drugs on arrhythmias was examined.

METHODS

Patient selection: Males or females, aged >21 years with signs and symptoms of CHF (NYHA classes II or III) were considered for entry into the study if they were on an optimal dose of digitalis and/or diuretics and were capable of performing 4–12 minutes of an exercise protocol on a bicycle ergometer. The underlying cause of the heart failure was not used to judge eligibility. The diagnosis of CHF was confirmed using chest radiograph (cardiothoracic ratio >0.5) or by radioisotope scan or echocardiography (ejection fraction $<45\%$).

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Patients were excluded from the study if they had a recent history of myocardial infarction or cardiac surgery (including percutaneous transluminal coronary angioplasty), or clinically important renal disorders. Patients with intrinsic lung disease or angina limiting exercise performance were also excluded, as were those with arrhythmias that required therapy other than with digoxin or amiodarone. Also excluded were those with any known hypersensitivities or other contraindications to ACE inhibitors. Local ethic committee approval for the study was obtained and patients gave informed consent for their participation. The study was conducted in accordance with the guidelines of the Declaration of Helsinki.

Study design: This was a double-blind, randomized, multicenter, parallel-group study. Randomization was preceded by a 10–14 day single-blind, placebo baseline period during which the digoxin and/or diuretic doses were optimized, all other vasodilator and ACE inhibitor treatment withdrawn, and placebo tablets matching lisinopril and enalapril (one each) were given once daily. At the end of the placebo run-in phase, patients were randomized to receive single doses of either 2.5 mg lisinopril or 2.5 mg enalapril. When possible, the day's diuretic treatment was withheld until after the ACE inhibitor had been given, to reduce the risk of first-dose hypotension. After successful initiation of therapy, the dose was increased to 5 mg once daily of either medication. If, after 2 weeks of randomized treatment, there was evidence of clinical improvement, treatment was maintained with the dose of 5 mg once daily for the remainder of the study. However, if there was evidence of a need for an additional therapeutic effect and standing systolic blood pressure was ≥ 90 mm Hg, and there were no symptoms of hypotension on the current dose, the dose of medication was increased to 10 mg once daily. At the end of 4 weeks of randomized treatment, the dose of drug could again be doubled, if necessary. The dose of medication could be reduced at any point during the study if the patient experienced symptomatic hypotension or any adverse event. A thorough physical examination of the patients was undertaken on entry into the study, and an abbreviated examination, review of symptoms, and assessment of the NYHA class of the patients by the same observer at each center was undertaken at randomization and repeated at the end of 12 weeks of randomized treatment. Standing blood pressure and heart rates were measured at each visit.

Concurrent medication with digitalis and/or diuretics was maintained throughout the study. When possible, the dosage of these drugs was the same or similar in both the randomized and run-in phases of the study. If a patient developed hypokalemia, potassium supplements were given with frequent monitoring of serum potassium levels. Potassium-sparing diuretics were not used in this study. No drugs affecting preload or afterload were allowed with the exception of long-acting nitrate therapy, which, when required, was kept constant throughout the study. Sublingual nitroglycerin was permitted. Anticoagulant treatment was permitted.

Exercise testing: Exercise capacity was assessed using an electrically braked bicycle ergometer. Patients began cycling on the bicycle at a workload of 20 watts for 1 minute at an average speed of 60 rpm, and this was increased by 10 watts every minute without any pause. Tests were discontinued if the patients manifested dyspnea, fatigue or exhaustion, anginal pain, muscle fatigue, or a progressive decrease in blood pressure or heart rate as exercise continued, or if heart rate exceeded the predicted age-related maximum level. Two exercise tests were performed during the run-in period. The first familiarized the patient with the procedure and the second was used as the baseline exercise capacity. During the randomized phase of the study, exercise capacity was measured after 6 and 12 weeks of treatment with either lisinopril or enalapril. Patients were asked to delay that day's study medication until after the exercise test, thus ensuring that the exercise tests were taken at the nadir of blood levels for both study medications.

Holter monitoring: Electrocardiographic Holter monitoring was performed for a 24-hour period during the placebo run-in and during the last week of randomized treatment; 24-hour electrocardiographic recordings were made using 2-channel Holter monitors. The analysis of the recording was performed electronically by Hertford Medical (Hertford, UK).

Blood chemistry: Blood samples obtained on entry to the study and at the end of 12 weeks' randomized treatment were taken for hematology, urea, electrolytes, and creatinine. At 2, 4, and 6 weeks of randomization, blood samples were analyzed for urea, sodium, potassium, and creatinine.

Adverse events: Volunteered side effects were obtained at each visit after the start of the placebo run-in period.

Statistical analysis: In this report the results of analysis of patients who completed the study

Table I Demographic Characteristics of Study Population at Randomization*

	Lisinopril	Enalapril
No. patients	138	140
Females (%)	19 (14)	27 (19)
Males (%)	119 (86)	113 (81)
Mean age (yr)	63 ± 10	61 ± 10
Age range (yr)	26–84	28–80
Body weight (kg)	75 ± 13	76 ± 14
Exercise capacity (seconds)		
All patients at entry	415 ± 133	449 ± 151
Prior to randomization	433 ± 119	462 ± 141
Etiology of heart failure† (%)		
Ischemic heart disease	85 (62)	88 (63)
Cardiomyopathy	47 (34)	46 (33)
Valvular heart disease	8 (6)	15 (11)
Hypertension	9 (6)	15 (11)
Other	6 (4)	4 (3)

*Data are mean ± standard deviation.
†Some patients had more than 1 contributory factor for heart failure.

(*completers analysis*) will be presented. The results and conclusions based on the *completers analysis* were found to be reflected in analyses based on alternative principles.

Analysis of covariance was used to compare lisinopril and enalapril effects for the change in exercise duration from the run-in visit to that after 6 and 12 weeks of treatment. The exercise duration at the run-in visit was used as the covariate. Analyses have been reported with respect to the comparison between lisinopril and enalapril using the t-test. Data are presented as mean value ± standard deviation and a p value < 0.05 was considered statistically significant.

To allow for variations in the duration of electrocardiographic recordings between different patients, the electrocardiographic data were converted to hourly rates for each recording. Only patients with a minimum of 8 hours of recording for both run-in and end of treatment assessment were analyzed. The effect of the 2 treatments on the hourly rate of arrhythmias was compared using the Wilcoxon rank sum test. The proportion of patients in each treatment group, with a reduction in the hourly rate of the ventricular ectopic counts from run-in to week 12 was compared using Fisher's exact test.

The proportion of patients who reported adverse events and those who withdrew due to adverse events were compared between lisinopril and enalapril treatments using Fisher's exact test. Because these analyses were concerned with treatment safety, all randomized patients were included.

RESULTS

Patients: A total of 300 patients entered the study from 37 centers; 22 patients were withdrawn during the placebo run-in phase and a further 29 withdrew while undergoing randomized treatment. The demographic characteristics of the patients randomized to treatment with enalapril or lisinopril are shown in Table I. In the majority of patients heart failure was due to ischemic heart disease or cardiomyopathy. When the available data from all patients were considered, it was apparent that the mean exercise capacity of enalapril patients at entry was 449 ± 151 seconds (mean ± standard deviation) and at the end of the run-in period was 462 ± 141 seconds compared with those randomized to lisinopril who at entry had an exercise capacity of 415 ± 133 seconds and 433 ± 119 seconds at the end of the run-in period. The difference at the end of the run-in period was not significant.

Exercise testing: The effects of lisinopril and enalapril treatment on exercise capacity of the patients after 6 and 12 weeks of treatment are shown in Figure 1. Exercise duration was significantly increased by both lisinopril and enalapril after 6 and 12 weeks of treatment, compared with their respective run-in exercise values. The mean time from the last dose to the exercise test for the enalapril and lisinopril treatment groups was 24 hours, 12 minutes and 26 hours, 29 minutes, respectively. The least-squares mean increase in exercise duration on lisinopril at 6 weeks was 30.1 seconds, and that for enalapril was 13.5 seconds. The increase in exercise duration was 16.5 seconds (95% confidence interval [CI], −5.6 to +38.6 seconds) more for lisinopril than enalapril after 6 weeks. The least-squares mean increase in exercise duration after 12 weeks was 65.1 seconds for lisinopril and that for enalapril was 41.9 seconds. The exercise duration was increased 23.2 seconds (95% CI, −2.3 to +48.8 seconds) more for lisinopril than enalapril after 12 weeks. There was no statistically significant difference between the 2 randomized treatments after 6 weeks ($p = 0.1415$) or after 12 weeks ($p = 0.0748$).

24-Hour Holter monitoring: The study revealed a very large variation in arrhythmic activity in this population. There were very small changes in the median hourly rates for ventricular ectopic counts, couplets, and nonsustained ventricular tachycardia after 12 weeks of treatment compared with run-in values, and the median changes were similar in each group. There were no significant differences between the treatments with respect to their effects

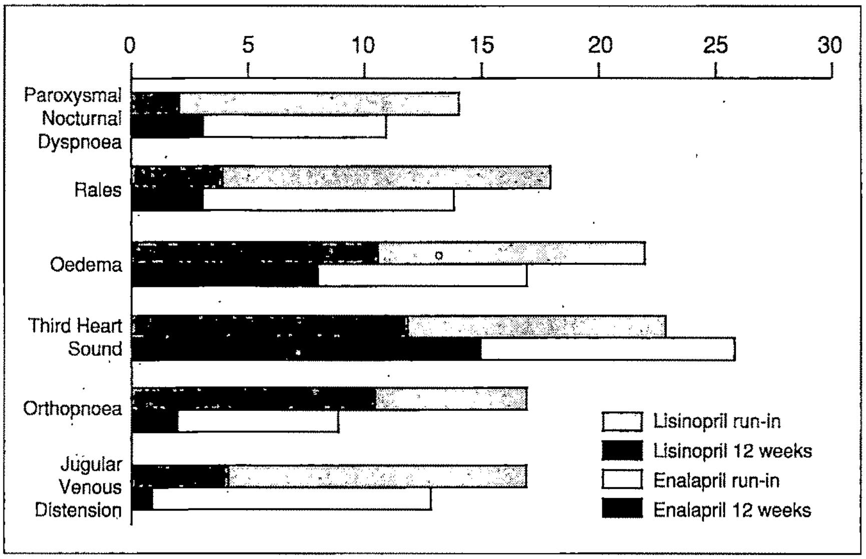

FIGURE 1. The effect of lisinopril or enalapril on the exercise capacity at the end of the run-in period and after 6 and 12 weeks of treatment. Data are presented as mean ± standard deviation.

on either ventricular ectopic counts (p = 0.1753), nonsustained ventricular tachycardia (p = 0.9390), or couplets (p = 0.0916). Of 83 patients who received lisinopril, 52 (63%), and 51 of 88 patients (58%) who received enalapril had a reduction in the hourly rate of ventricular ectopic counts at week 12 of treatment, compared with the run-in value. This difference was not significant.

NYHA classification: The proportion of patients with different grades of heart failure before and after treatment with either lisinopril or enalapril are shown in Table II, together with the proportion of patients on each treatment in whom changes in NYHA grade were seen. No differences were observed between the 2 treatments.

Symptom review: Figure 2 shows the percentage of randomized patients presenting with similar symptoms of CHF, both at run-in and after 12 weeks of randomized treatment with either lisinopril or enalapril. Both drugs improved the monitored symptoms, and the effects of treatment were similar for both treatment groups.

Blood pressure and heart rate: Blood pressure and heart rates were similar for both treatment groups throughout the duration of the study. Neither treatment had any significant effect on heart rate or systolic and diastolic blood pressures compared with baseline values.

Blood chemistry: Routine hematology and biochemistry studies revealed no significant changes overall during randomized treatment with either drug although there was a tendency for serum potassium concentration to increase on both treatments. Notably, neither ACE inhibitor treatment in this study produced a significant change in renal function (assessed serum creatinine or urea).

Adverse events: A total of 15 patients in the enalapril treatment group withdrew from the study; 8 cases withdrew because of adverse reactions. In the lisinopril treatment group, 14 patients

Table II New York Heart Association (NYHA) Classification and Changes in NYHA Class in Patients Receiving Lisinopril or Enalapril for 12 Weeks

	Lisinopril (%)	Enalapril (%)
Before treatment		
NYHA class II	58	64
NYHA class III	42	36
After treatment		
NYHA class I	18	20
NYHA class I and II	—	2
NYHA class II	69	69
NYHA class III	12	9
NYHA class IV	1	—
Change with treatment		
Improvement	48	43
No change	49	53
Deterioration	3	2

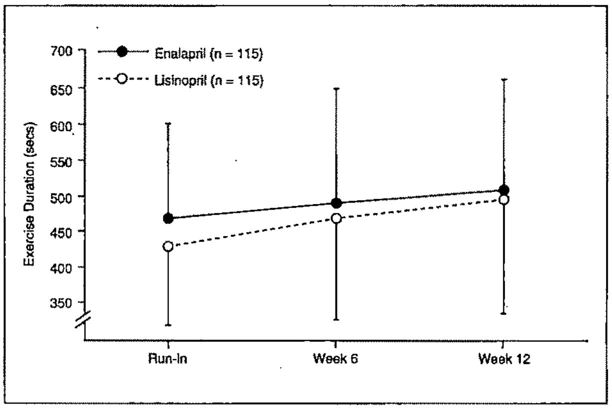

FIGURE 2. Percentage of patients with symptoms of heart failure present at run-in and after 12 weeks of randomized treatment with lisinopril and enalapril. Numbers in parentheses indicate the number of patients in each group.

Table III Adverse Events and Other Reasons Leading to Withdrawal

Reason	Lisinopril	Enalapril
Angina pectoris	1	—
Cardiac arrest/sinus arrest	1	—
Cardiomyopathy	—	1
Coma	1	—
Conduction disturbances	—	1
Diarrhea	1	—
Dizziness/lightheadedness	3	1
Dyspnea	—	1
Edema, pulmonary	1	1
Electrocardiographic abnormalities	—	1
Epileptiform attack	1	—
Fall in blood pressure	1	2
Fibrillation	1	—
Fractured ankle	1	—
Gastric discomfort	—	1
Hematuria	1	—
Hospitalization	1	4
Hyperkalemia	1	—
Lumbago	1	—
Malaise	1	—
Mitral valve disorder	—	1
Myocardial infarction	2	3
Nausea	—	1
Pacemaker	—	1
Pain in hip	1	—
Palpitations	—	1
Prostatectomy	—	1
Rash, pruritus	—	2
Renal colic	1	—
Unconsciousness	—	1
Unwell	1	—
Weight gain	—	1

withdrew, 12 due to adverse reactions. Table III lists the adverse reactions that led to withdrawal from randomized treatment. Overall, the most commonly reported adverse events were cough, dizziness, fall in blood pressure, vertigo, and myocardial infarction. The most common symptoms reported spontaneously by the patients during randomized treatment were dyspnea, dizziness, cough, and angina. There were no significant differences between the treatments with respect to the incidence of spontaneously reported symptoms, side effects, or withdrawal from therapy.

DISCUSSION

This study is one of the largest comparisons of ACE inhibitors in heart failure undertaken to date. Enalapril is most often used twice daily in heart failure. However, 1 study has demonstrated that enalapril's effects are the same, whether given as a single or divided dose.[11] Since its early development, lisinopril has been used only once daily and it was of interest to compare these similar ACE inhibitors when both were used once daily for they have very similar pharmacokinetic half-lives and a long duration of action. The pharmacokinetic half-life of lisinopril is 12.6 hours,[15] compared with 11.1 hours for enalapril.[14] This small difference has been shown to produce a slightly longer duration of action for lisinopril, when equal doses of the 2 drugs were given.[16] There is also some evidence of a slightly more sustained hemodynamic effect with lisinopril compared with enalapril in normal volunteers given equal doses of the 2 drugs.[17]

In the present study, exercise capacity was assessed at the end of the dosing interval, when any small differences in duration of action of such similar drugs may be anticipated to become manifest. However, no significant difference between the drugs was apparent. In this context it is worth noting that the mean time from the last dose to the exercise test for the enalapril group was 24 hours, 12 minutes compared with 26 hours, 29 minutes for lisinopril patients (difference not significant). It has been suggested that treatment with the highest tolerated doses for a period of at least 3 months may be required to demonstrate fully the beneficial effects of therapy and to eliminate training and placebo effects in the study population.[18]

Because this study incorporated a dose titration phase as part of the treatment period this design may have made differentiation of the 2 trial drugs more difficult.

Neither drug had any significant impact on ventricular ectopic activity. Although the use of median values may give the impression that there was no ventricular tachycardia in these patients, the range of frequency of arrhythmias was extremely wide and no effect of drug treatment could be discerned.

Both treatments improved the NYHA grading and the frequency of monitored symptoms to a very similar degree. Both drugs were well tolerated to an equal extent in this study and there were no unexpected findings with regard to the pattern of adverse events.

In conclusion, the results of this study indicate that lisinopril 5–20 mg once daily is at least as effective and well tolerated as enalapril 5–20 mg once daily. Neither ACE inhibitor treatment in this study produced a significant change in patients of renal function (serum creatinine or urea) in contrast to observations comparing a short- and long-acting ACE inhibitor in heart failure.[19] Because exercise capacity was measured at a point in time at which the blood levels and pharmacologic activity of both drugs would be minimum, the small differences observed between the response to the 2 drugs may reflect the difference between the 2 drugs with regard to their duration of action as ACE inhibitors. Lisinopril is a useful addition to therapeutic options for the treatment of CHF.

APPENDIX

Members of the study group were as follows. **The Netherlands:** K.I. Lie, A. Taekens, L.E.J.M. Schrijvers, E.W. Van Den Toren (Delfzijl); J.J. de Graaf (Drachten). **France:** M. Dallocchio (Pessac); M. Bory (Marseilles); J.P. Richalet (Grenoble); J.P. Bounhoure (Toulouse); G. Barthelemy (Mantes La Jolie). **Belgium:** Y. Devaleriola, C. Philippart (La Louviere); C. Deceuninck (Mouseron); J-M Chaudron (Haine St Paul); D.E.L. Allaf (Huy); L. Desplanque (Tournai); P. Collignon, V. Boudinet, H. Joris (Liege); J. Pirlet (Boussu); R. Nicolas (Herstel); L. Humblet (Seraing); X. Dalle (Antwerp); R. Popeye (Verne); J. Beys, U. Van Walleghem (Mechelen); R. Zenner (Dendermonde). **Norway:** E. Soyland (Oslo); C. Von Brandis (Stavanger); J.E. Otterstad, E. Frisland (Vestfold); T. Morstol (Alesund); J.E. Nordrehaug (Bergen); J. Haerem (Hamar). **Portugal:** M. Carreia (Lisbon). **Ireland:** M. Laher (Dublin). **Spain:** J. Bruguera (Barcelona); F. Garcia-Fernandez (Madrid); A. Cortina (Oviedo).

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Comparison of Lisinopril Versus Digoxin for Congestive Heart Failure During Maintenance Diuretic Therapy

Johan Herlitz, MD, PhD, on behalf of the Lisinopril–Digoxin Study Group

Lisinopril 5–20 mg once daily was compared with digoxin 0.125–0.375 mg once daily in a double-blind, randomized, parallel-group study involving 217 patients with mild-to-moderate heart failure (New York Heart Association [NYHA] grades II–III) who were maintained on optimized diuretic therapy. After 6 weeks of treatment, digoxin and lisinopril had increased exercise duration by 18 seconds ($p = 0.015$) and 32 seconds ($p = 0.0007$), respectively, versus the baseline run-in period. The difference between treatments was not statistically significant ($p = 0.1343$). After 12 weeks, digoxin and lisinopril had increased exercise duration by 29 seconds and 51 seconds, respectively. The effect of digoxin compared with the baseline value was not significant but that for lisinopril was ($p = 0.0027$). The difference between treatments approached statistical significance ($p = 0.0813$). There was no difference between lisinopril and digoxin with regard to their effects on the frequency of ventricular ectopic counts, couplets, or nonsustained ventricular tachycardia. Blood pressures were not significantly different between treatments, although both systolic and diastolic blood pressure were consistently lower in the lisinopril group throughout randomized treatment. The proportions of patients demonstrating an improvement in NYHA grading were similar for both lisinopril and digoxin. Both treatments had similar effects on the symptoms of heart failure. Both drugs appeared to be equally well tolerated with a similar frequency of adverse events reported for both drugs (30% for lisinopril vs 29% for digoxin). Withdrawals from treatment were of a similar frequency for both treatments. It is concluded that lisinopril may be a useful alternative to digitalis in patients with heart failure who remain symptomatic on diuretic therapy.

(Am J Cardiol 1992;70:84C–90C)

For some years, angiotensin-converting enzyme (ACE) inhibitors have been recognized as being effective in the management of congestive heart failure (CHF) when added to previous therapy with optimum doses of digitalis and diuretics.[1,2] Currently, there is increasing interest in the possibility that ACE inhibitors may be used earlier in the treatment of CHF.[3] However, in order to replace traditional first-line therapy of CHF, ACE inhibitors must be established to be superior to, or at least as effective as, the current first-line agents, digitalis or diuretics.

Digitalis has a narrow therapeutic ratio and there is a consequent risk of digitalis toxicity especially in the elderly.[4] Several studies have compared digitalis and ACE inhibitors in the treatment of mild heart failure.[5–10] The studies concerning the short-acting ACE inhibitor captopril have shown comparable or slightly greater exercise capacity with the ACE inhibitor than with digitalis.[5–8] Single studies comparing enalapril versus digoxin and lisinopril versus digoxin indicate similar results.[9,10] The principal aim of this study was to compare the effects of the long-acting ACE inhibitor lisinopril with the effects of digoxin on exercise capacity in patients with mild-to-moderate CHF who were already receiving optimum doses of diuretics. A secondary aim was to examine the effects of lisinopril and digoxin on the spectrum of arrhythmias seen in patients with mild-to-moderate CHF.

METHODS

Patients: Following informed consent patients were recruited for this study at 21 centers in 5 countries: Denmark (2), Sweden (12), Spain (3), United Kingdom (1), Austria (3). Male or female

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patients >21 years old with the clinical signs and symptoms of CHF of New York Heart Association (NYHA) grades II and III were considered eligible for entry into the study. The diagnosis of CHF was based on clinical signs and symptoms supported by the use of chest radiograph, radioisotope scan or echocardiography. Criteria for inclusion were age >21 years, either sex, clinical signs and symptoms of CHF, NYHA grade II or III, cardiothoracic ratio >0.5 or ejection fraction <45%, normal sinus rhythm, and capable of 4–12 minutes graded exercise on bicycle ergometry. Exclusion criteria from participation were myocardial infarction, cardiac surgery (including percutaneous transluminal coronary angioplasty), cerebrovascular accident, unstable angina (all within the preceding 3 months); severe angina-limiting exercise capacity; standing systolic blood pressure <90 mm Hg or >160 mm Hg; right heart failure; fixed rate cardiac pacemaker fitted; atrial fibrillation or other arrhythmias requiring therapy; history of liver, blood, or endocrine disorders; clinically important renal disorder and abnormal serum potassium; history of drug or alcohol abuse; and hypersensitivity or other contraindications to ACE inhibitors or digoxin. All patients were maintained on stable doses of diuretics. The study was conducted in accordance with the Declaration of Helsinki, and local ethical committee approval was obtained.

Study design: Lisinopril and digoxin were compared using a double-blind, parallel-group, randomized, multicenter study design, which is depicted in Figure 1. A double-dummy technique was used to maintain blindness. The study incorporated a baseline period of 10–14 days, during which time the diuretic dosage was optimized in the absence of vasodilator therapy. Patients were then randomized to either lisinopril or digoxin for 12 weeks. At randomization, all patients received a test dose of lisinopril (2.5 mg). Symptoms reported or experienced by the patients were fully documented. Those randomized to lisinopril thereafter received lisinopril 5 mg once daily for 2 weeks initially. Those patients randomized to receive digoxin received 0.125 mg once daily for 2 weeks initially. If, after 2 weeks of the randomized treatment, there was evidence of clinical improvement, the patient continued on that dosage. An increase in the dosage of study medication was considered after 2 weeks of randomized treatment, and again after a further 2 weeks of randomized treatment.

The dose was increased if, in the opinion of the investigator, there was evidence of a need for an additional effect and provided that the following 2 safety conditions were met: standing systolic blood pressure was ≥90 mm Hg and there were no symptoms of hypotension (syncope, faintness, orthostatic effects, dizziness) on the current dose. When an increase in the dosage of study medication was indicated, lisinopril dosage was first increased to 10 mg once daily and finally to a maximum of 20 mg once daily. The dosage of lisinopril was reduced at any relevant visit if the patient exhibited symptomatic hypotension or any other adverse event. An increase in the dosage of digoxin to 0.250 mg once daily was considered after 2 weeks of randomized treatment if there was need for further efficacy and the previously mentioned safety conditions were met. If, after a further 2 weeks of treatment, the dosage of digoxin warranted an increase, the dosage was increased to a maximum of 0.375 mg once daily. This dosage of digoxin was not considered appropriate for patients aged >65 years or those weighing <50 kg. As a consequence, these patients were not given the highest dose of digoxin or lisinopril permitted in the protocol, i.e., no more than 0.250 mg of digoxin. If a side effect appeared that was believed to be attributable to overdosage of digoxin, the dose could not be reduced, but rather the patient was withdrawn from the study,

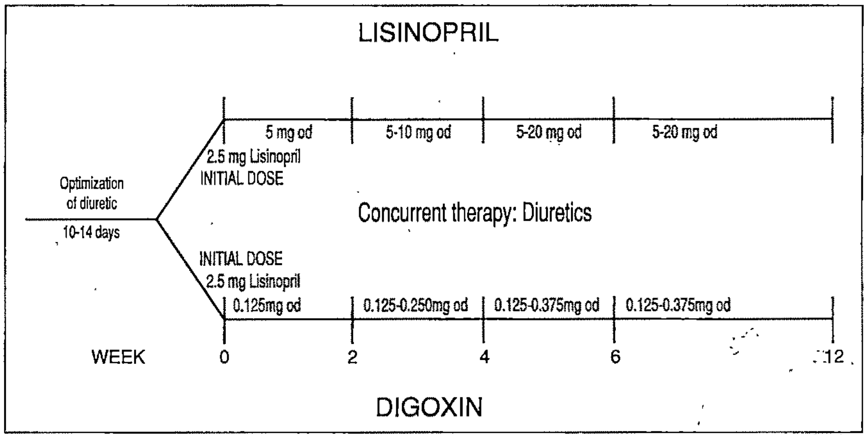

FIGURE 1. Schematic representation of the study design and dose titration schedule. od = once daily.

without breaking the double-blinded nature of the treatment.

Concurrent medication: During the randomized phase of the study, the aim was to maintain patients on the same or similar regimen of diuretics as they received during the baseline period. However, the diuretic dose could be adjusted during the randomized treatment phase if needed, based on the clinical assessment. The morning dose of diuretic was withheld on the day the patient received the test dose of lisinopril and potassium-sparing diuretics were not permitted during the study. If a patient developed hypokalemia, potassium supplements were administered with monitoring of serum levels. Chronic nitrate therapy, when used, was kept constant, and additional sublingual nitroglycerin was permitted as required. No other drugs known to affect preload or afterload were allowed.

Clinical assessment: A complete physical examination of each patient was conducted at the time of entry into the study. An abbreviated symptom review and physical examination was performed at randomization and at the end of 12 weeks of randomized treatment. Exercise testing was performed using an electrically braked bicycle ergometer, and followed a schedule with continuous incremental work loads. All patients underwent a bicycle exercise test on 2 separate occasions during the placebo run-in, prior to entry into the randomized treatment phase of the study. The first exercise test served as a familiarization procedure for the patient. The second exercise test enabled the duration of exercise to be determined. If the duration of the 2 exercise tests differed by more than 2 minutes, a third test was required before proceeding to randomization. Exercise tests were also carried out after 6 and 12 weeks of randomized treatment. Patients undertook each exercise test at the same time of day (preferably in the morning), and medication was delayed on the day of the exercise test until measurements were complete. Blood pressure was measured at each clinical visit on the same arm, using a mercury sphygmomanometer. Heart rate was measured on each visit by palpation of the radial pulse over a 30-second period. Recordings of blood pressure and heart rate were made after the patient had been standing for 2 minutes. Classification of the patient according to the NYHA criteria was done by the same observer at the end of the placebo run-in period and again after 12 weeks of randomized treatment.

Holter monitoring was performed for a 24-hour period during placebo run-in and during the last week of randomized treatment using a 2-channel Holter monitor. Analysis of all the 24-hour tapes was performed electronically by Hertford Medical (Hertford, UK). Only data from patients with at least 8 hours of monitoring for the run-in and end of treatment examinations were summarized and analyzed.

Blood samples were obtained at entry to the study and after 12 weeks of randomized treatment for hematology and biochemical assessments. Blood samples were taken after 2, 4, and 6 weeks of randomized treatment for biochemical assessment only. Full blood count and an estimation of urea, sodium, potassium and creatinine were carried out.

Reports of side effects were elicited at each visit after the start of the placebo run-in period using a nonleading question, and the nature and severity of any symptoms reported were noted. Patients were asked to bring any unused tablets with them at each visit to assess compliance. Patients with evidence of tablet consumption <50% or >150% of the prescribed dose were considered to have deviated from the study protocol.

Statistical analysis: It was calculated that 172 patients (86 per group) would be required to detect a mean difference between treatments in exercise duration of 60 seconds. This calculation was made at the 5% level of significance, with 90% power and using a standard deviation of 120 seconds. To allow for withdrawals from the study, it was intended that 250 patients (125 per group) would take part in the study.

Analysis of covariance was used to compare lisinopril and digoxin for the change in exercise duration from the run-in visit to treatment week 6 and the change from the run-in visit to that at treatment week 12.

The results reported below are based on an analysis of data from patients for whom complete data were available both at run-in and after 12 weeks of treatment (*completers analysis*). The analyses have been reported with respect to the comparison between lisinopril and digoxin using the *t*-test.

The proportion of patients in each treatment group with a reduction in the hourly rate of ventricular ectopic counts after 12 weeks of treatment was compared between lisinopril and digoxin using Fisher's exact test.

The proportion of patients with adverse reactions and the proportion who withdrew due to adverse reactions were compared between lisinopril and digoxin using Fisher's exact test. Because these analyses were concerned with treatment safety, all randomized patients were included in this analysis.

TABLE I Demographic Variables of the Study Population Randomized to Either Lisinopril or Digoxin Therapy*

	Lisinopril	Digoxin
No. patients	107	102
Females (%)	31 (29)	19 (19)
Males (%)	76 (71)	83 (81)
Mean age (yr)	63 ± 10	62 ± 11
Age range (yr)	38–82	35–94
Body weight (kg)	73.7 ± 11.6	76.5 ± 13.3
Etiology of heart failure† (%)		
Ischemic heart disease	66	69
Cardiomyopathy	22	25
Valvular heart disease	17	8
Hypertension	10	12
Other	2	4
Exercise capacity (seconds)		
All patients at entry	445 ± 138	463 ± 141
Prior to randomization	446 ± 128	468 ± 140

*Data are presented as mean ± standard deviation.
†Some patients had more than 1 contributing factor for heart failure.

TABLE II Proportion of Patients with Changes in Exercise Capacity and NYHA Grading after 12 Weeks of Treatment with Lisinopril or Digoxin Compared with Baseline

	Lisinopril (%)	Digoxin (%)
Exercise capacity		
Increased	66	56
No change	9	9
Decreased	25	35
Before treatment		
NYHA grade II	76	75
NYHA grade III	23	25
After treatment		
NYHA grade I	5	6
NYHA grade II	82	81
NYHA grade III	12	13
NYHA grade IV	1	—
Change with treatment		
Improvement	17	16
No change	78	81
Deterioration	5	2

NYHA = New York Heart Association.

RESULTS

A total of 217 patients entered the study. Of these, 8 patients withdrew during the run-in period. After the run-in period, 107 patients were randomized to receive lisinopril and 102 patients were randomized to receive digoxin. The demographic data for the 2 randomized groups of patients are shown in Table I. Duration of exercise at the entry and run-in visits was found to be higher for the patients randomized to receive digoxin than for the patients randomized to lisinopril. As a guide, significance tests were carried out to compare the treatment groups at entry and run-in. Neither of these tests was significant at the 20% level ($p > 0.2$).

During active treatment, the proportions of patients on low (5 mg), medium (10 mg), and high (20 mg) daily doses of lisinopril were 33, 44, and 23%, respectively. The corresponding proportions for the patients in the digoxin-treated group were 29, 44, and 27%, respectively. Thus, any imbalance between the 2 groups with regard to baseline exercise capacity does not appear to be reflected in any change in the relative proportions of the drug dosages used.

The effects of lisinopril and digoxin treatments on exercise duration after 6 and 12 weeks of treatment are shown in Figure 2. After 6 weeks of treatment there was a significant improvement in mean exercise duration from run-in, for both the digoxin and lisinopril treatment groups. Digoxin treatment increased exercise duration by 18 seconds ($p = 0.015$) and lisinopril treatment increased exercise duration by 32 seconds ($p = 0.0007$). The difference between the mean improvements on each of the treatments was small. Similarly, 12 weeks of randomized treatment with lisinopril or digoxin improved exercise capacity compared with their respective run-in values. Digoxin treatment increased exercise capacity by 29 seconds, and lisinopril treatment improved exercise capacity by 51 seconds compared with exercise capacity at baseline. This effect with digoxin was not statistically significant, but that for lisinopril was ($p = 0.0027$). Mean treatment difference at 12 weeks was 27 seconds. However, this difference did not reach significance ($p = 0.081$). After 12 weeks of treatment, 66% of patients improved their exercise time on lisinopril treatment compared with 56% on digoxin (Table II). The percentages of patients who showed decreased exercise capacity

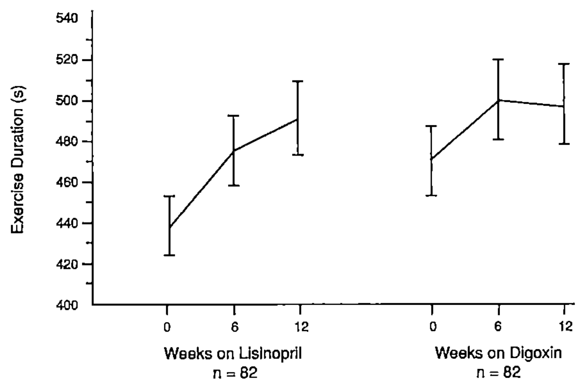

FIGURE 2. The effect of lisinopril or digoxin on exercise capacity at the end of the run-in period and after 6 and 12 weeks of treatment. Data are presented as mean ± standard deviation. There were 82 patients in each group.

TABLE III Effect of 12 Weeks of Treatment with Lisinopril or Digoxin on Arrhythmic Activity

Arrhythmic Activity	Lisinopril (n = 78)	Digoxin (n = 70)
Ventricular ectopic counts (VECs)		
Patients with > 5 VEC/min (%)		
At end run-in	10.2	12.8
After 12 weeks of treatment	6.4	10.0
Patients showing change (%)		
Decrease	59	46
No change	0	0
Increase	41	54
Couplets		
Patients with couplets (%)		
At end run-in	69.2	65.7
After 12 weeks of treatment	68.0	55.7
Patients showing change (%)		
Decrease	45	39
No change	21	26
Increase	35	36
Nonsustained ventricular tachycardia (VT)		
Patients with nonsustained VT (%)		
At end run-in	35.9	31.4
After 12 weeks of treatment	23.1	25.7
Patients showing change (%)		
Decrease	31	27
No change	56	53
Increase	13	20

n = number of patients in analysis.

after 12 weeks of lisinopril or digoxin treatment were 25% and 35%, respectively.

24-Hour electrocardiographic monitoring: The proportion of patients who exhibited ventricular ectopic counts, couplets, and nonsustained ventricular tachycardia both before and after treatment with lisinopril or digoxin together with the percentage of patients in whom the frequency of arrhythmias changed on treatment are summarized in Table III. Of 78 patients who received lisinopril, 46 (59%), and 32 of 70 patients (46%) who received digoxin had a reduction in the hourly rate of ventricular ectopic counts from run-in to treatment week 12. There was no significant difference between lisinopril and digoxin for these proportions.

Blood pressure: Blood pressure was unaffected by digoxin treatment. At the end of the run-in period, blood pressure was 133 ± 18/82 ± 9 mm Hg, and after 12 weeks of treatment, it was 135 ± 19/82 ± 9 mm Hg. Heart rate was similarly unaffected, decreasing from 83 ± 12 beats/min at the end of the run-in period to 80 ± 13 beats/min after 12 weeks of treatment with digoxin. On lisinopril treatment, blood pressure fell slightly but not significantly from 132 ± 20/81 ± 12 mm Hg at the end of the run-in period to 127 ± 20/79 ± 11 mm Hg after 12 weeks of treatment. Heart rate was unchanged (82 ± 13 beats/min at run-in compared with 81 ± 13 beats/min after 12 weeks of lisinopril treatment).

NYHA grading: The proportion of patients with the different grades of heart failure before and after treatment with either lisinopril or digoxin is shown in Table II together with the proportion of patients on each treatment in whom changes in NYHA grade were seen. No differences were observed between treatments.

Symptoms and signs of CHF: The percentage of patients in whom particular symptoms of heart failure were present at run-in and after 12 weeks of randomized treatment is shown in Figure 3. For the most part, the 2 treatments were indistinguishable, except possibly for edema, where a higher proportion of patients treated with digoxin (13%) appeared to experience a loss of the symptom,

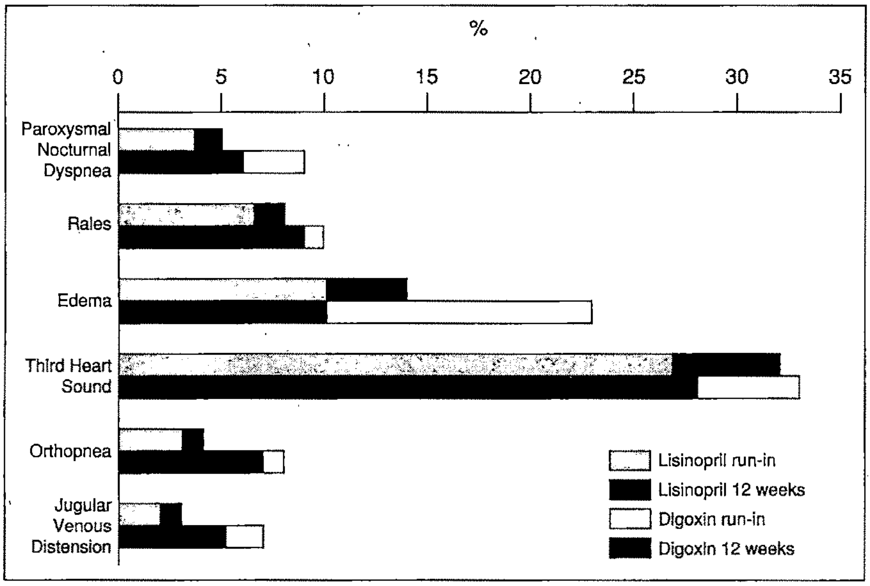

FIGURE 3. Percentage of patients with symptoms of heart failure present at run-in and after 12 weeks of randomized treatment with lisinopril and digoxin. The bars represent the percentage of patients in each treatment group in whom this sign or symptom was present at run-in and after 12 weeks of treatment. In the lisinopril-treated group the percentage of patients with paroxysmal noctural dyspnea increased after 12 weeks of treatment compared with the end run-in assessment.

TABLE IV Adverse Events Reported in > 1% of Patients Randomized to Either Lisinopril or Digoxin

	Lisinopril (n = 107)		Digoxin (n = 102)	
	n	%	n	%
Death	1	0.9	3	2.9
Cough	12	11.2	1	1.0
Nausea	3	2.8	6	5.9
Dizziness	4	3.7	4	3.9
Fatigue	2	1.9	3	2.9
Dyspnea	3	2.8	1	1.0
Myocardial infarction	3	2.8	1	1.0
Vertigo	3	2.8	1	1.0
Cardiac arrhythmias	1	0.9	2	2.0
Hypotension	3	2.8	0	0.0
Chest pain	3	2.8	0	0.0

compared with a smaller number (4%) on lisinopril treatment.

Adverse events: Adverse reactions were reported for 30 of 107 patients (28%) who received lisinopril and for 30 of 102 patients (29.4%) who received digoxin (Table IV). The most frequent adverse events reported for digoxin were nausea, dizziness, fatigue, and death. The pattern was different in the lisinopril group, with cough, dizziness, nausea, dyspnea, vertigo, myocardial infarction, hypotension, and chest pain being reported as the most frequent adverse events. One patient died during lisinopril treatment due to myocardial infarction and there were 3 deaths in the digoxin-treated group (due to myocardial infarction in 2 patients and sudden death in 1 patient).

Withdrawals from therapy due to adverse reactions occurred for 9 out of 107 patients (8.4%) who received lisinopril and for 11 of 102 patients (10.7%) who received digoxin. Side effects leading to withdrawal are listed in Table V. There was no significant difference between lisinopril and digoxin with regard to the proportion of patients who withdrew due to adverse reactions. One patient withdrew from the study because of deterioration in the disease, and one patient failed to attend for evaluation in the digoxin group. Two patients in the lisinopril-treated group and two patients in the digoxin group withdrew from the study after randomization for reasons other than adverse reactions.

DISCUSSION

There was a small imbalance in the 2 treatment groups at randomization with regard to baseline exercise duration. However, it appears that this did not interfere with the conduct of the study or with the overall conclusions of it. There was also a slight imbalance with regard to the proportion of men in the digoxin group (81%) compared with the lisinopril group (71%). This difference was not significant but a slightly higher proportion of men in the digoxin group might have contributed somewhat to the better run-in exercise time in the digoxin group.

TABLE V Incidence of Deaths and Adverse Events During 12 Weeks of Treatment with Lisinopril or Digoxin

	Lisinopril (n = 107)		Digoxin (n = 102)	
	n	%	n	%
Death	1	0.9	3	2.9
Withdrawals	12	11.2	18	17.6
Adverse events				
Leading to withdrawal	9	8.4	11	10.7
Not leading to withdrawal	20	18.7	16	15.7

When added to background treatment with diuretics, the effect of 12 weeks of treatment with lisinopril or digoxin on exercise capacity were not significantly different. Both treatments improved exercise capacity after 6 weeks of treatment with respect to baseline but no significant difference between treatments was found. Thus, this study demonstrates a similar effect on exercise duration for both the ACE inhibitor and digoxin. In this regard this study is consistent with the majority of those previously reporting on comparisons of other ACE inhibitors and digoxin,[5–9] and with a smaller, earlier study in which lisinopril and digoxin were compared.[10] The data presented in Figure 2 suggest little improvement in exercise capacity was achieved with digoxin between weeks 6 and 12, perhaps implying that its initial effects may not be sustained. Exercise duration on digoxin was not significantly different after 12 weeks of treatment compared with the baseline value. Doubts have been expressed regarding the long-term efficacy of digoxin in heart failure and its value has been doubted in the presence of sinus rhythm. Although it now appears to be effective in the presence of good sinus function, its role is much clearer in the presence of atrial fibrillation.[4]

In this study, both lisinopril and digoxin treatment produced an improvement in exercise capacity in a similar proportion of patients and both treatments were also similar with regard to their effect on the global NYHA grading of patients.

The addition of lisinopril or digoxin to baseline treatment with diuretics produced a reduction in the ectopic activity exhibited by some patients, but there was no significant difference between treatments for the hourly rates of ventricular ectopic counts, couplets, and nonsustained ventricular tachycardia after 12 weeks of treatment.

Blood pressure did not decline significantly and heart rate was not affected by either of the 2 study treatments. These latter observations have been made previously for lisinopril (see Zannad et al and Bach and Zardini, elsewhere in this symposium), and it is reassuring that the ACE inhibitor treatment was not associated with a marked decrease in blood pressure.

There was a more marked reporting of cough as a side effect to lisinopril in this study compared with other studies, in which lisinopril was compared to other ACE inhibitors (see Zannad et al and Bach and Zardini). This may suggest that cough may go relatively unrecognized during treatment with an ACE inhibitor, and its presence in the population is more clearly recognized when a non-ACE inhibitor comparator is used in the study. The design of the study, necessitating the withdrawal of any patient suspected of a side effect attributable to digoxin overdose rather than dose reduction, may have resulted in the withdrawal of some lisinopril-treated patients.

CONCLUSION

The results of this study indicate that when added to diuretic treatment both lisinopril and digoxin improved exercise duration after 12 weeks of treatment with no significant difference between treatments. When compared with baseline values, there was a significant increase with lisinopril but not with digoxin. Both drugs can be safely added to diuretics in patients with mild to moderate heart failure. Lisinopril seems to be a useful alternative to digoxin in this clinical situation.

APPENDIX

Members of the study group were as follows.

Sweden: J. Herlitz, B. Karlson (Göteborg); K. Boman, L. Wikström (Skelleftea); P-O Bengtsson, M. Freitag (Karlskrona); A. Rindner (Skene); J.E. Frisell (Ludvika); K-A Svensson (Ljungby); J. Jonsson, C. Nemeczek, (Varberg); B. Ritter, H. Wingman (Östersund); S. Hansen, S. Ekdahl, (Eksjö); P. Lantz, J. Landelius (Uppsala); P. Smedgård (Skövde); D. Ursing, U. Ahremark (Ängelholm). **Denmark:** S.L. Rasmussen, R. Videbaek (Hvidovre); E. Vigholt (Aarhus). **Austria:** H. Mayr, J. Bergler-Klein (Vienna); W. Klein, J. Dusleag (Graz). **Spain:** L.M. Elbal, C. Saenza de la Calzada (Madrid); F. Algarra (Valencia). **United Kingdom:** R. Wray (Hastings).

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Safety of Long-Term Use of Lisinopril for Congestive Heart Failure

Christopher Moyses, MRCP, DM, and Trevor J.C. Higgins, PhD

Early clinical experience with lisinopril suggested that it was well tolerated in congestive heart failure (CHF). An analysis of data from >1,000 patients treated with lisinopril has been performed to examine the long-term safety of lisinopril in CHF. Of these, 620 have been studied for up to nearly 4 years, and a further 440 have been studied in comparative trials for 3 months. When patients who received lisinopril or placebo for the same period were compared, the proportion of lisinopril patients reporting an adverse event was 44.1% compared with 39.4% on placebo. Over a 4-year period, 205 patients (33.1%) discontinued treatment. About 33% of these died, 33% withdrew due to clinical adverse events, 21 (3.4%) were withdrawn because of adverse laboratory findings, and 56 (9.0%) withdrew for reasons unrelated to treatment. Sixteen patients (2.6%) withdrew because lisinopril was deemed ineffective. The most frequently reported drug-related adverse laboratory findings were increases in blood urea nitrogen, blood urea, serum creatinine, and plasma potassium. There appeared to be no differences in the pattern of adverse events with respect to the race of the patient. Elderly patients and those with the most severe forms of heart failure appeared to be at greater risk for an adverse event. Evaluation of the safety of lisinopril compared with enalapril, captopril, and digoxin in controlled clinical trials shows all the angiotensin-converting enzyme inhibitors to be equally well tolerated with a closely similar range of adverse events, suggesting that the satisfactory safety profile of lisinopril is shared by other drugs of this class. Lisinopril appears to be well tolerated in the treatment of heart failure.

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Since their introduction, the angiotensin-converting enzyme (ACE) inhibitors have become a cornerstone of the management of congestive heart failure (CHF).[1] There is now substantial evidence that the use of these drugs prolongs life[2,3] as well as producing symptomatic improvement[4,5] and improvements in hemodynamics.[4,6] Indeed, as a class, the ACE inhibitors have been shown to be more effective in reducing mortality than some other vasodilator regimens.[3] Because the control of symptoms of these patients represents one of the therapeutic goals of treatment, the adverse effects of the drugs used in the management of CHF and the risk–benefit balance of therapy is an issue worthy of consideration. Adverse effects of treatment gathered from controlled clinical trials, in carefully selected and monitored patients, give much valuable information regarding the risks of treatment.

Lisinopril (ICI 209,000) was first registered in 1987 and became available for general use in 1988. The early clinical trial experience with lisinopril in 311 patients with mild-to-moderate heart failure[7] showed a mortality similar to that on placebo with causes of death typical of heart failure patients. The most commonly encountered adverse events were dizziness, diarrhea, and hypotension (Figure 1) and the major causes of discontinuation were hypotension, dizziness, renal impairment, rash, and diarrhea. Since that time, lisinopril has been further evaluated in controlled clinical trials in patients with CHF.

As use of a new drug expands and its use becomes widespread in situations outside that of the controlled clinical trial, other unsuspected adverse effects may appear. The aim of this review is to assess the safety and tolerability of lisinopril as it applies specifically to the patient with CHF, both in controlled clinical trials and in the context of widespread general use.

METHODS

Patients: Patients with CHF in clinical trials were in functional classes II–IV on the New York

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Heart Association (NYHA) grading system, and the vast majority received concurrent treatment with diuretics and/or digitalis. Spontaneous reports of adverse events have concerned patients with a wide range of severity of heart failure who were taking a wide range of concurrent medications.

Safety assessment: This review of safety encompasses adverse events recorded during controlled clinical trials, during open-label extension studies, and those arising from spontaneous reports during marketed use; the methods by which adverse reactions are collected in these situations are necessarily different.

In the controlled clinical studies, involving 620 patients, adverse clinical experiences were sought at each visit in all studies, and the subjects were required to report any event that seemed unusual, whereupon they were questioned about the nature of each event. The clinical investigators were made aware of the result of earlier clinical studies, both by discussion and by use of a brochure containing information regarding lisinopril.

An event was considered to be serious if it was a definite hazard or handicap to the patient and any relation between the adverse event and the use of lisinopril was graded by the investigator, using a 5-point scale (definitely not, probably not, possibly, probably, or definitely drug related).

All adverse events from these studies experienced by patients while taking lisinopril have been considered for inclusion in this review up to the time when the drug was first marketed. Except where indicated, this was irrespective of the opinion of the investigator regarding any causal relationship to the use of lisinopril.

Many of these controlled trials were extended so as to evaluate the safety of long-term exposure of patients to lisinopril, and additional patients were recruited into the controlled phases of the studies, thereby extending their power. As a result, a recent analysis of data from 620 patients treated with lisinopril has been possible. The scope of the present review encompasses long-term safety of lisinopril in the treatment of CHF, but because the occurrence of adverse events may be anticipated to increase with increased time of exposure to the drug, it is appropriate to consider the frequency of adverse events on lisinopril treatment compared with placebo during the initial 12-week double-blind phase of the evaluation of the drug, as well as the effects of long-term exposure.

In addition, 4 double-blind, parallel-group clinical studies, each of 12 week duration (vide infra), have recently been completed. This has provided tolerability data for lisinopril in a further 440 patients and has allowed comparison of lisinopril with enalapril, captopril, and digoxin. In the case of these studies, adverse events were reported only for the controlled phases of these trials.

Once the drug is marketed, reliance is necessarily placed on spontaneous reports from physicians and information passed to the company by regulatory authorities who have been informed of adverse events by physicians in their own country. In the case of these reports, some information regarding the patient's condition and other possible contributory factors, such as the other drugs being

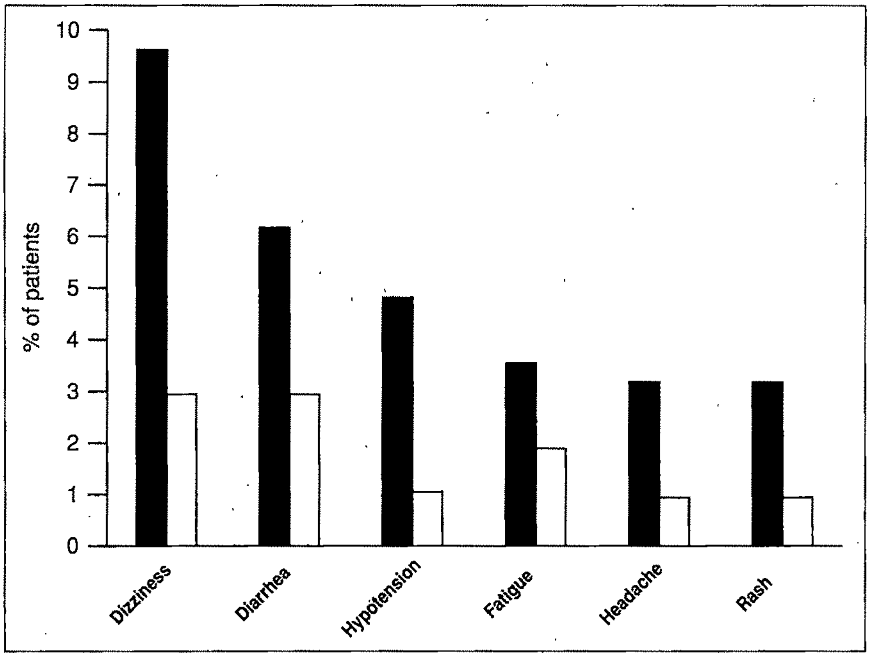

FIGURE 1. Early adverse experiences occurring in ≥3% of patients with CHF in the lisinopril and placebo treatment groups. Filled bars = lisinopril (n = 311); open bars = placebo (n = 104). CHF = congestive heart failure.

TABLE I Demographic Data for Heart Failure Patients Receiving Lisinopril

	No. Patients (%)
Total	620
Sex	
Male	476 (77%)
Female	144 (23%)
Age (yr)	
18–34	20 (3%)
35–44	49 (8%)
45–54	119 (19%)
55–64	244 (39%)
65–81	188 (30%)
Mean age (yr)	58.5
Race	
Caucasian	540 (87%)
Black	66 (11%)
Other	14 (2%)
Etiology	
Coronary heart disease	226 (36%)
Valvular heart disease	43 (7%)
Cardiomyopathy	220 (35%)
Hypertension	43 (7%)
Other	40 (6%)
Unknown	48 (8%)
Duration of heart failure	
<1 year	216 (35%)
1–5 years	256 (41%)
6–10 years	64 (10%)
>10 years	33 (5%)
Unknown	51 (8%)
New York Heart Association class	
I	1 (0.2%)
II	198 (32%)
III	299 (48%)
IV	71 (11%)
Unknown	51 (8%)

used, may be missing or inadequately reported. Additionally, when some adverse effects of treatment are well recognized and are already listed in the prescribing information for the drug, there may be a reluctance on the part of physicians to report these adverse effects, with a consequent emphasis (of uncertain extent) on reporting unusual or unexpected adverse events.

TABLE II Frequency of Clinical Adverse Events Occurring in ≥1% of Heart Failure Patients Taking Lisinopril During Double-Blind, Placebo-Controlled Studies

	Lisinopril (n = 313) %	Placebo (n = 155) %
Death	2.9	5.2
Body as a whole		
Abdominal pain	2.2	1.9
Asthenia	3.8	3.2
Chest pain	3.2	1.3
Edema	1.0	0.6
Malaise	1.3	0.0
Orthostatic effects	1.0	0.0
Syncope	1.3	0.6
Cardiovascular system		
Angina pectoris	1.6	3.2
Hypotension	5.1	0.6
Orthostatic hypotension	1.0	0.0
Palpitation	1.0	0.0
Digestive system		
Diarrhea	4.2	1.9
Nausea	2.6	5.2
Vomiting	1.3	0.6
Metabolic/nutrition/immune		
Weight gain	1.0	0.0
Nervous/psychiatric		
Dizziness	13.4	4.5
Headache	5.1	3.9
Paresthesia	1.0	0.0
Respiratory system		
Cough	2.2	2.6
Dyspnea	3.2	4.5
Upper respiratory infection	1.0	1.3
Skin and skin appendages		
Alopecia	1.0	0.6
Erythema	1.0	0.6
Pruritus	1.0	1.9
Rash	1.9	0.6
Urogenital system		
Renal dysfunction	1.0	0.0

RESULTS

Patients: The demographic characteristics of the population of 620 patients are presented in Table I. Duration of treatment with lisinopril ranged from a single dose to approximately 4 years. The mean duration of treatment was 321 days overall. Total exposure to lisinopril was 199,112 patient days. The lisinopril-treated population was predominantly male and 69% of the population was aged ≥55 years. The majority (87%) were Caucasian. The most common causes of heart failure were coronary artery disease (36%) or cardiomyopathy (35%); 41% of patients had had heart failure for 1–5 years but 35% of the population had the syndrome for <1 year. The majority of the patients had NYHA class II or III heart failure.

Comparison with placebo: Data comparing the incidence of adverse effects on lisinopril to that on placebo during 12 weeks of double-blind treatment are shown in Table II. Adverse events are categorized by the body system in which they occurred. Most frequently affected were the body as a whole, the nervous and psychiatric system, the cardiovascular system, and the respiratory and digestive systems. When patients who received lisinopril and placebo for the same period were considered, the percentage of lisinopril patients who reported an adverse event (44.1%) was similar to that percentage reporting adverse events on placebo (39.4%). The most frequently reported adverse events on lisinopril were dizziness, hypotension, headache, diarrhea, and asthenia. Interestingly, death, heart failure, dyspnea, and nausea were seen on placebo more frequently than on lisinopril therapy.

TABLE III Incidence of Adverse Events Affecting the Different Body Systems*

Body System	Lisinopril (n = 620) %
Body as a whole (includes deaths)	26.5
Cardiovascular system	21.1
Digestive system	16.3
Endocrine	0.5
Hemic and lymphatic system	0.6
Metabolic/nutritional/immune	3.5
Musculoskeletal system	7.7
Nervous and psychiatric	21.6
Respiratory system	20.3
Skin and skin appendage	9.7
The senses	4.0
Urogenital system	7.1

*Mean duration of exposure to lisinopril was 321 days.

Extended use of lisinopril: In the extended use of lisinopril for up to 4 years, the most frequently affected body systems were the body system as a whole, the cardiovascular, respiratory, nervous and psychiatric, and digestive systems (Table III). The most frequently reported adverse events were dizziness, dyspnea, chest pain, asthenia, cough, diarrhea, hypotension, and nausea (Figure 2). Some of these events are also characteristic of the patient population with CHF and for this reason many of the reports of some adverse effects, e.g., dyspnea, were only rarely considered to be drug related by the attending physician.

Deaths and discontinuation of therapy: Of the 620 patients treated with lisinopril, 73 (11.8%) died during the survey period. Overall, 205 patients discontinued lisinopril treatment (33.1%). About 33% of these patients died and about 33% withdrew due to adverse clinical events. Of the patients who stopped treatment, 21 (3.4%) were withdrawn because of adverse laboratory test results; 16 (2.6%) withdrew because lisinopril was deemed ineffective, and 56 (9.0%) were withdrawn for reasons unrelated to treatment.

The major causes of death during lisinopril therapy were the same as those reported in the earlier smaller scale surveys,[7,8] primarily sudden death, myocardial infarction, worsening CHF, and cardiogenic shock. Only 2 deaths (1 sudden death and 1 renal failure) were thought to be possibly drug-related by the attending physicians.

The most frequent clinical events necessitating withdrawal are depicted in Figure 2, along with the most frequently reported adverse events. Hypotension, dizziness, and rash were the most common causes of discontinuation of lisinopril in CHF patients.

Serious nonfatal adverse events: Serious, but nonfatal, adverse events were experienced by 110 of 620 patients (17.7%). Some of these patients subsequently died, but these adverse events were usually distinct from the final cause of death.

Adverse laboratory findings: The major changes observed in laboratory parameters believed to be drug-related were increases in blood urea nitrogen, blood urea, and serum creatinine (Table IV). Increases in serum potassium are an anticipated effect of ACE inhibitors, due to their action in suppressing aldosterone release. Changes in liver enzyme titers and in urinary protein excretion are features encountered in patients with CHF and have been observed in the use of other ACE inhibitors.[9]

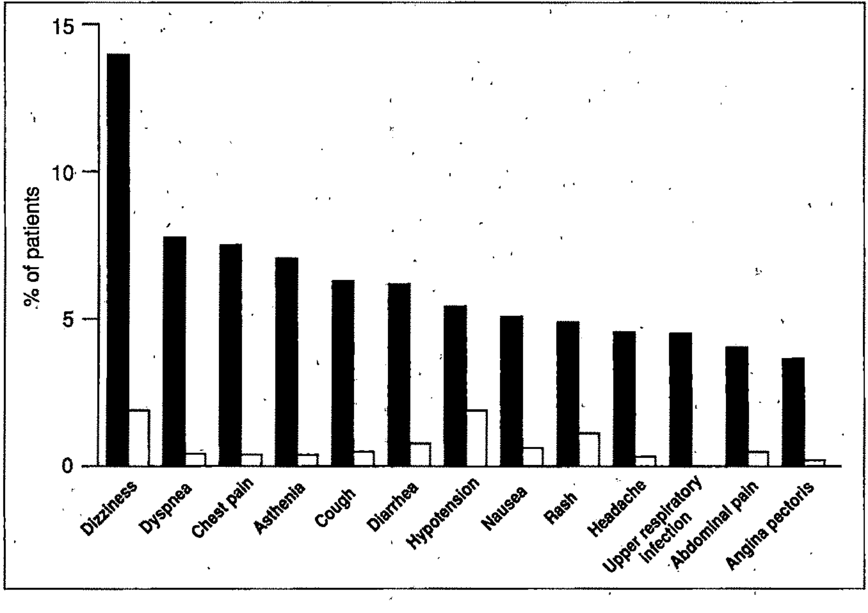

FIGURE 2. Adverse experiences occurring in ≥3% of heart failure patients treated with lisinopril. The frequency of adverse events is shown in filled bars and withdrawals by open bars. The total number of patients was 620 and mean duration of treatment was 321 days.

Overall, 3.4% of patients were withdrawn from treatment because of adverse laboratory findings. Most of these were considered to be drug-related by the investigators. Changes in hematologic values and elevations in serum creatinine, serum potassium, and urinary protein have been observed during the treatment of CHF patients with other ACE inhibitors, notably captopril and enalapril.[10–12]

During the course of these studies, 9 of 582 patients (1.6%) had hemoglobin values <10 g/dL, or 6.2 mmol/liter. None was discontinued, and in 3 patients the values returned to normal during the observation period. One of 584 patients (0.2%) had total white blood cell counts <2,500 mm^3. This was considered an isolated observation, and the white blood cell count was >2,500 mm^3 during the rest of the study. Two of 350 (0.6%) had a platelet count <100,000 mm^3.

Of 591 patients 34 (5.8%) had serum creatinine >2.5 mg/dL (221 mmol/liter). Elevation of serum creatinine, especially when ACE inhibitor treatment is combined with diuretic treatment in CHF patients, is well established.[11,12] The clinically important elevations occurred most often in patients with abnormal values at baseline and were frequently transient in nature.

Of 292 patients 9 (3.1%) had urinary protein excretion >1,000 mg/24 hour. Most of these patients exhibited the abnormality during baseline therapy. One patient was withdrawn.

Special groups—effect of age, race, renal function, and severity of heart failure: The adverse events encountered during these studies have been examined with respect to subsets of patients who might be considered to represent a different risk from treatment with lisinopril compared with the general population.

In order to consider the possibility that the elderly were at a particular risk from treatment with this drug, the total study population (620) was divided into those aged ≥65 years (n = 188) and <65 years (n = 432): 18% of the elderly subgroup and 15% of the younger patients continued treatment for >2 years, and the mean duration of treatment was 347 and 310 days for the elderly and the young subsets, respectively. Although the incidence of death or nonfatal serious events does not seem substantially different between the 2 groups, the elderly appear to be at a higher risk of discontinuation due to an adverse event.

Of the 620 patients in the studies, only 66 were Black. However, no apparent differences between the Black and Caucasian patients were observed with respect to the safety of lisinopril treatment.

TABLE IV Most Frequent Laboratory Adverse Findings Occurring in >0.5% of Heart Failure Patients Treated with Lisinopril and Considered to Be Drug-Related by the Investigator*

	% of Patients in Whom Measured	
Finding	Drug-Related by Investigator	All Patients
Hematocrit reduced	0.6	1.3
Blood urea nitrogen increased	7.7	13.9
Blood urea increased	2.3	3.0
Serum creatinine increased	6.2	10.9
Serum bilirubin increased	0.6	0.9
Serum AST increased	1.1	4.4
Serum ALT increased	0.9	3.4
Serum uric acid increased	1.7	5.0
Serum potassium increased	3.0	4.8
24-hour urinary protein increased	4.3	4.3

*Mean duration of treatment 321 days
ALT = alanine aminotransferase; AST = asparate aminotransferase.

Renal function has been an important issue in the use of ACE inhibitors since their introduction, and abnormalities of renal function are not uncommon in the general CHF patient population. Thus, the safety of lisinopril in the renally impaired patients is of particular interest.

The total population was divided into those with baseline serum creatinine levels ≥1.6 and <1.6 mg/dL. Patients with more advanced renal failure (>2.5 mg/dL) were excluded from clinical study and so systematic information regarding the safety of lisinopril in this subgroup of patients is lacking at present.

A subset of 85 patients with serum creatinine ≥1.6 mg/dL were treated for a mean period of 432 days and 420 patients with normal renal function (serum creatinine <1.6 mg/dL) were treated for a mean of 334 days (in 115 patients the baseline serum creatinine values were not known). Although the incidence of death appears lower in those with renal impairment than in those with normal renal function, the incidence of adverse events, including nonfatal serious ones appeared to be higher in those with renal impairment.

When the patients were stratified by severity of CHF using their baseline NYHA grades, it was observed that the incidence of adverse experiences of all severities, as well as the incidence of death, tended to increase with the severity of CHF. This finding would be anticipated from existing knowledge of the risks of death from heart failure.[13] When the duration of treatment with lisinopril was taken into account, the incidence of death, especially in the NYHA class IV patients, seemed somewhat lower than previously reported.[14]

Comparative safety: Four recently reported double-blind, parallel-group clinical trials (see Bach and Zardini, Zannad et al, Herlitz, and Sloman elswhere in this symposium) in which lisinopril has been compared with captopril (2 trials), enalapril and digoxin have provided data on comparative safety (Figure 3). The most frequent adverse events appear to be common to all 4 drugs and may reflect the symptoms of CHF as much as the effects of therapy. The ACE inhibitors all have a remarkably similar adverse-event profile, suggesting that the adverse events seen in these trials reflect class effects of these drugs.

One particular feature of these comparative data deserves comment. In a comparative study of lisinopril and captopril (see Bach and Zardini in this symposium) it was noted that blood urea and serum creatinine values were affected to a similar extent by both the long-acting and short-acting ACE inhibitor, suggesting that sustained ACE inhibition is not generally associated with impaired renal function in heart failure patients.

Spontaneous reports of adverse events: The spontaneous reports so far received from general clinical worldwide use of lisinopril in heart failure suggest a pattern of adverse events similar to that observed in this clinical trial population, which has been the subject of intense study and which is reported here. Reports of adverse events cluster most frequently in: the genitourinary system, where deterioration in renal function, including renal failure, is the most prominent adverse event; in the cardiovascular system where hypotension, including first-dose hypotensive events, is the more frequent observation; and in adverse reactions involving the skin, where rashes and angioedema are reported. Isolated cases of thrombocytopenia and neutropenia have been reported, although in such cases the data are inadequate to establish any causal link with the drug.

DISCUSSION

Previous evaluations of lisinopril have demonstrated it to be well tolerated in the treatment of CHF.[7,8] This report is based on increased numbers of patients studied and increased duration of treatment with lisinopril and also encompasses general use of the drug in the uncontrolled situation. Data collected in the open-label use of lisinopril without a placebo control tend to increase artificially the incidence of adverse events recorded during treatment. As heart failure is of a generally symptomatic nature, longer follow-up periods tend to lead to the recording of more adverse events. Because of the number of drugs being taken by heart failure patients, it is more difficult to assign a causal relation between an adverse event experienced by a patient and lisinopril treatment.

Overall, this review of safety and tolerability of lisinopril in heart failure leads to the conclusion that it is generally well tolerated in such patients and that clinical adverse events usually do not require discontinuation of therapy. The incidence of death in patients with heart failure is 2.9% in those treated with lisinopril, compared with an

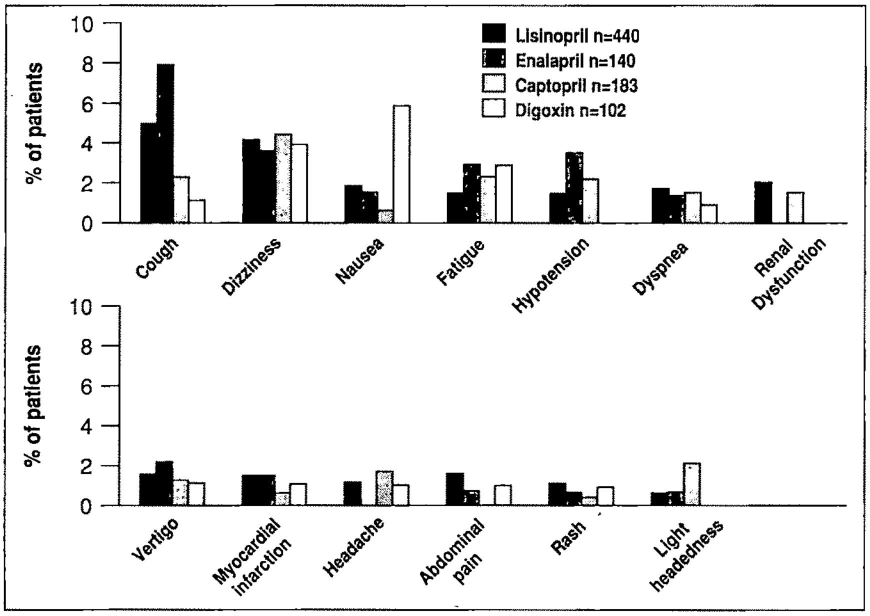

FIGURE 3. Incidence of adverse events occurring in >1% of heart failure patients in controlled comparative trials of lisinopril, enalapril, captopril, and digoxin. Deaths, worsening heart failure, and resulting hospitalizations have been omitted.

incidence of 5.2% in the control group treated with placebo during 12-week double-blind trials. This contrasts with the very early clinical experience that showed a very similar mortality rate for both lisinopril and placebo. The most frequent clinical adverse experiences observed are dizziness, dyspnea, chest pain, asthenia, cough, diarrhea, and hypotension.

The percentage of heart failure patients discontinuing lisinopril due to an adverse clinical event within a treatment period of 4 years is 11%, and this was attributable primarily to hypotension, dizziness, and lack of response. The most frequently reported adverse laboratory findings in lisinopril-treated patients included elevations in blood urea nitrogen or blood urea, serum creatinine, and serum potassium. Changes in laboratory values in lisinopril-treated patients were generally minor and seldom resulted in discontinuation of therapy.

Although the overall incidence of adverse events was generally higher in patients receiving long-term therapy with lisinopril, reflecting the longer exposure to the drug, there were no unusual or unexpected adverse events. Many of those that occurred have also been recorded for other ACE inhibitors and may well be class related.[14] No outstanding differences with regard to the safety of lisinopril have been observed in older versus younger patients, Black versus White patients, or in those with renal impairment or severe heart failure.

A recent comparative study of lisinopril and captopril (see Bach and Zardini in this symposium) has shown no difference between the 2 drugs with regard to blood urea and serum creatinine values. This observation suggests that use of the longer-acting ACE inhibitor was not generally associated with renal impairment, as was suggested by the early work of Packer et al[15] using higher doses of ACE inhibitors and diuretics. In an earlier comparative study, Giles et al[16] demonstrated a greater tendency for lisinopril to increase blood urea nitrogen values than did captopril, although the drugs did not differ significantly in their tendency to increase serum creatinine.

In conclusion, this survey of data on 620 patients together with new, additional comparative data on a further 440 patients in double-blind trials and >3 years of spontaneous reports confirms earlier observations[7,8] regarding the generally well-tolerated nature of lisinopril when used once daily for the treatment of CHF in addition to established therapy with digitalis and/or diuretics.

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Importance of Long-Acting Angiotensin-Converting Enzyme Inhibitors for Congestive Heart Failure

Thomas D. Giles, MD

The renin–angiotensin system (RAS) has both localized and systemic effects in the pathophysiology of heart failure. These may lead to structural changes in the heart and blood vessels as well as to more disseminated symptomatology, including vasoconstriction and both salt and water retention. In association with other neurohormonal mechanisms, such as the sympathetic nervous system, these latter effects result in an elevated work load for the heart. The increase in neurohormonal activity, seen in some patients with heart failure, may result in a loss of circadian variation in heart rate and blood pressure and deprive the heart of a needed reduction in work load during the night. The suppression of such neurohormonal activity through the use of long-acting angiotensin-converting enzyme (ACE) inhibitors, such as lisinopril, provides a means of controlling such symptoms. In comparison with short-acting ACE inhibitors, such long-acting suppression of the RAS may have a number of advantages. These include a more sustained increase in exercise duration, improvement in left ventricular ejection fraction, and, speculatively, a better influence on patient mortality.

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The cardiovascular system is wonderfully responsive in meeting the needs of the body for blood flow. The orchestration of flow to various vascular domains is complex and involves at least the autonomic nervous system, including both the sympathetic and parasympathetic nervous systems and endothelium-derived factors, such as endothelium-derived constricting factor, endothelium-derived relaxing factor, and endothelium-derived hyperpolarizing factor. Throughout the day, alterations in these factors vary the work load on the heart by changes in heart rate, impedance to ventricular ejection, and myocardial contractility. Variations in physical activity and neurohumoral systems produce a circadian variation in many cardiovascular functions: heart rate, systemic arterial blood pressure, cardiac output, blood volume, and viscosity. Thus, in normal individuals heart rate and blood pressure reach their peak during the daylight hours, gradually decline at night, and then rise quickly beginning just prior to and continuing during the working hours until they reach a peak again.[1]

When the heart becomes diseased and begins to develop diastolic and systolic dysfunction, changes occur in the autonomic nervous system and various neuroendocrine systems.[2,3] Parasympathetic withdrawal occurs first, perhaps manifested by an increase in resting heart rate, followed by sympathetic nervous system activation. In this stage of heart failure, there may be maintenance of the circadian variation in blood pressure and heart rate. As heart failure becomes more advanced, the renin–angiotensin system (RAS) becomes activated, as do the endothelial systems and secretion of vasopressin.[3,4] These systems produce vasoconstriction and salt and water retention, despite the production of counter regulatory neurohormonal systems, such as atrial natriuretic peptide and vasodilator prostaglandins.[5] The circadian varia-

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tion in blood pressure and heart rate may also be diminished.

RENIN–ANGIOTENSIN SYSTEM IN HEALTH AND HEART FAILURE

The RAS appears to serve an endocrine, as well as a paracrine and autocrine, function in the cardiovascular system.[6–8] The endocrine RAS is primarily concerned with maintaining intravascular volume and sodium homeostasis, whereas the physiologic role of the tissue RAS is less clearly understood, but may be associated in the heart with myocardial growth and architectural changes.[9] During exercise, the RAS becomes activated and in the normal subject may serve to facilitate sympathetic nervous system activity.[10]

The RAS becomes activated in patients with heart failure when the dysfunction is sufficiently severe that the heart cannot simultaneously meet the demands of the numerous circulatory beds.[11] The blood flow to "less important" vascular beds, such as that in the skin, is reduced first. At some point, blood flow may be reduced to working skeletal muscle, particularly during exercise.[12] Derangement in neurohumoral function, including the RAS, may be responsible for interfering with normal cardiovascular reflexes (for example, during upright exercise, constriction of forearm blood flow).[13]

CONSEQUENCES OF NEUROHUMORAL ACTIVATION IN HEART FAILURE

The consequences of neurohumoral activation in heart failure impinge on both the heart and the peripheral circulation.[1] The increased cardiac work load due to vasoconstriction and salt and water retention may result in further cardiac damage and remodeling; such changes may result in inexorable cardiac failure.

The effects of a reduction in blood flow to working skeletal muscle are seen in deconditioning and further limitation of exercise ability.[11] Limitation of blood flow to skeletal muscle, together with increased cardiac filling pressures and reduced cardiac output, result in the symptoms of dyspnea and fatigue.[1] Inexorable heart failure results in generalized cellular dysfunction with death ensuing from terminal arrhythmias or complications, such as infections or pulmonary embolism. Wide swings in neurohumoral activation may be associated with sudden death, since there is an increased incidence of these events during the early morning and waking hours.[14]

THERAPEUTIC STRATEGY BASED ON EXCESS NEUROHUMORAL ACTIVATION AND ALTERED CIRCADIAN VARIATION

The goals of therapy in heart failure include relieving symptoms and prolonging life. Interruption of excess neurohumoral activation would seem an attractive means to achieve these goals; a decrease in heart rate, impedance to ventricular ejection, and a decrease in cardiac filling pressures would decrease cardiac work load and perhaps induce the heart to decrease in size. Improvement in skeletal blood flow at rest and during exercise would restore those changes associated with conditioning and increase exercise capacity. Alteration of the inexorable heart failure would prolong life and a decrease in neurohumoral surges might protect against sudden death. The pharmacologic approach to interruption of the neurohumoral systems in heart failure has involved various vasodilators, but most attention has been focused recently on the angiotensin-converting enzyme (ACE) inhibitors and the combination of a nitrate and hydralazine.

For cardiac unloading to be of maximal benefit and the opportunity for muscle reconditioning, interruption of excessive neurohumoral activation should occur continuously. Moreover, constant interruption would perhaps offset potential adverse autocrine or paracrine effects.

CLASSIFICATION OF ACE INHIBITORS

ACE inhibitors are classified according to the presence, or absence, of a sulfhydryl group, the need for metabolic conversion to an active compound, i.e., a prodrug or not, the affinity for the ACE, and the degree of tissue penetration.[15] These chemical properties account for the differing pharmacodynamic properties of the ACE inhibitors and their classification as short acting (duration of action of a single oral dose of <24 hours), or long acting (duration of action >24 hours).

The only short-acting ACE inhibitor currently in use in clinical practice for the treatment of heart failure is captopril.[16] Whether administered orally or intravenously,[17] the maximum hemodynamic effect of captopril occurs within 2 hours and the total duration of action is 6–8 hours. Lisinopril and enalapril are ACE inhibitors whose hemodynamic effects last for ≥24 hours following an oral dose.[15]

The contrasting pharmacodynamic activities of the short- and long-acting ACE inhibitors are reflected in a large multicenter trial comparing the effects of lisinopril with those of captopril in

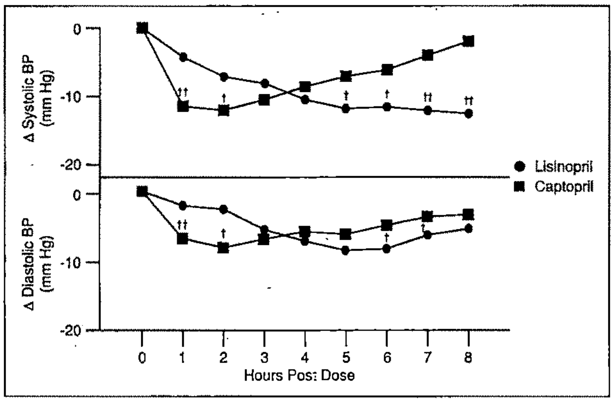

FIGURE 1. A comparison of the effects of the angiotensin-converting enzyme (ACE) inhibitors lisinopril and captopril on systemic systolic and diastolic arterial blood pressure as a function of time postdose. BP = blood pressure.

patients with heart failure (Figure 1).[18] The effects of captopril on systemic systolic and diastolic arterial blood pressure peak at 2–2.5 hours and are no longer present at 8 hours after the initial dosing. In contrast, the effects of lisinopril are still present 8 hours after dosing.

IS LONG-ACTING ACE INHIBITION BENEFICIAL IN HEART FAILURE?

Almost all clinical trials of the efficacy of ACE inhibitors in heart failure report that both long- and short-acting ACE inhibitors increase exercise duration. However, exercise tests in heart failure trials are usually conducted at the expected "peak" effect of the short-acting ACE inhibitor. This timing may be of importance, since the dynamic action of activation of the RAS during exercise may be influential in limiting blood flow to working skeletal muscle.[10] Thus, in a clinical trial comparing the effect of captopril with that of nicorandil on exercise duration in heart failure, captopril improved exercise duration at "peak" effects, but failed to do so at "trough" effects.[19] Thus, prolonged ACE inhibition may be required if exercise improvement is expected throughout the day.

The time course of ventricular unloading may differ among the short- and long-acting ACE inhibitors. Alterations in cardiac loading conditions may be reflected in the calculated left ventricular ejection fraction. Thus, in clinical trials of ACE inhibitors in heart failure, left ventricular ejection fraction determinations may be obtained without attention being paid to the "peak" and "trough" effects of the drugs. This may explain the lack of improvement in left ventricular ejection fraction noted for the short-acting ACE inhibitor, captopril and the improvement observed in patients treated with the long-acting ACE inhibitor, lisinopril.[18]

TABLE I Potential Effects of Long-Acting Angiotensin-Converting Enzyme Inhibitors

Potential Beneficial Effect	Potential Negative Effect
Constant suppression of pathophysiologic process	Constant interruption of normal physiology
Convenience for patients	Development of drug tolerance
Improved compliance	Peak effect necessary to achieve long duration of action
Prevention of vulnerable periods during which a sudden exacerbation of the disease process can occur	
Possible increased cost-effectiveness	

Differences in mortality rates between those treated with short- and long-acting ACE inhibitors have also been reported in clinical trials of positive inotropic agents. In the study of xamoterol, a β-adrenoceptor antagonist with intrinsic sympathomimetic activity, mortality was higher among those patients receiving captopril compared with those receiving enalapril or lisinopril.[20]

The effects of the long-acting ACE inhibitors in patients with heart failure may be potentially positive or negative (Table I). The most frequently reported adverse effect attributable to long-acting ACE inhibitors has been that of renal insufficiency, from examples of constant interruptions of renal physiology.[21] This usually takes the form of an increase in blood urea nitrogen, with a smaller increase in serum creatinine concentration. These changes reflect the effect of a lowered systemic arterial blood pressure, coupled with the selective effect of the ACE inhibitors on the efferent arteriole of the glomerulus, thereby decreasing glomerular filtration rate. These effects are usually of little clinical consequence and the safety profile of the long-acting ACE inhibitors has been impressive.[22] Excess diuresis should be avoided to minimize the problem. It was also feared that prolonged and sustained hypotension would occur with the long-acting ACE inhibitors. However, this fear has not been borne out. Developement of drug tolerance has not been reported from patients receiving ACE inhibitors for treatment of heart failure and serious hypotension has been an infrequent occurrence.[22]

CONCLUSIONS

The time course of variation in cardiac work load as determined by systemic arterial blood pressure and heart rate has important implications for the heart. The pharmacodynamic pattern of drugs used to treat heart failure must be superimposed on this circadian pattern of hemodynamic, and other changes. The importance of the RAS in the pathophysiology of heart failure has been established, with the interruption of this system by the ACE inhibitors having been proven to be beneficial for patients by improving signs, symptoms, exercise duration, and mortality. It appears that constant suppression of the RAS in heart failure may be desirable to enhance exercise capacity, unload the heart throughout the day, and perhaps have a better influence on mortality. These effects are achievable with the long-acting ACE inhibitors.

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Differences in Structure of Angiotensin-Converting Enzyme Inhibitors Might Predict Differences in Action

Arnold G. Herman, MD, PhD

Angiotensin-converting enzyme (ACE) inhibitors probably work by inhibition of tissue-located ACE, and they differ with regard to their relative ability to inhibit ACE in different organs. This apparent tissue selectivity may stem from either differences in tissue bioavailability or from a different affinity for the enzyme. The affinity of the ACE inhibitor for a particular enzyme is not only determined by the structure of the inhibitor, but also by the structure of the enzyme. ACE enzymes from different tissues may be slightly different, and this may have some bearing on the relative affinities of different ACE inhibitors for ACE from different tissues. The duration of inhibition in a particular tissue reflects not only the affinity of that inhibitor for the tissue enzyme, but also reflects the ease or difficulty with which the active ACE inhibitor is released from that tissue. Whether the beneficial effects of ACE inhibitors on experimentally induced myocardial infarction and reperfusion arrhythmias are due to the presence of a sulfhydryl group or are mainly related to the ACE inhibitor-mediated bradykinin potentiation remains a matter of controversy.

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Since angiotensin-converting enzyme (ACE) inhibitors produce a decrease in blood pressure in a number of situations in which plasma renin levels are low and since there appears to be no correlation between the decrease of inhibition of plasma ACE and the duration of the ACE inhibitor's antihypertensive effects, it is now generally accepted that these drugs work by inhibition of tissue-located ACE. There is accumulating evidence that inhibition of vascular ACE in resistance vessels, large arteries, and veins may contribute to the therapeutic actions of the ACE inhibitors.

Further, it has been suggested that ACE inhibitors differ with regard to their relative capacity to inhibit ACE in different organs and this could be of particular interest in view of the actions of angiotensin II as a growth factor and stimulator of cell division,[1,2] thereby contributing to the development of hypertrophy and vascular remodeling.[3,4]

Here we will discuss how this apparent tissue selectivity as well as the differences in the duration of action of the various ACE inhibitors could be related to the differences in their structures.

CHEMISTRY

The current clinically studied ACE inhibitors have varying chemical structures. They include the sulfhydryl group-containing compounds captopril and zofenopril, the carboxyalkyl dipeptides enalapril, lisinopril, ramipril, benazepril, cilazapril, perindopril, and quinapril, and the phosphinic acid fosinopril (Figure 1). Differences in structure may result in differences in pharmacokinetics, pharmacodynamics, and side effects.

PHARMACOKINETICS

Absorption: Absorption of a drug from the gastrointestinal tract is very much determined by its lipophilicity: the more lipid soluble the drug is, the more easily it crosses the cell membrane barriers in order to pass from one compartment,

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i.e., the gastrointestinal lumen, to the plasma compartment. Lipophilicity of a drug is mainly related to its structure and to the degree of ionization at a given pH.

In addition to other structural differences, all of the above-mentioned ACE inhibitors, with the exception of captopril and lisinopril, are esters of the active compounds (prodrugs) that are more lipophilic than the parent compounds and are therefore more quickly and completely absorbed. The active forms of the drugs reach a peak level in the serum in 1–4 hours after ingestion, depending on whether the agent is administered as a prodrug or as an active drug. For example, captopril reaches a peak level 1 hour after ingestion, whereas enalaprilat, the active metabolite of enalapril, peaks at 4 hours. The bioavailability of the various compounds, i.e., the fraction of the dose administered that reaches the systemic circulation after absorption from the gastrointestinal tract and passage through the liver, varies between 25% (lisinopril) and 70% (captopril). Despite these large differences, it is not of much clinical importance, as long as the intrapatient or interpatient variability of the amount of the drug absorbed is not too high, which is not the case for the ACE inhibitors. However, it should be taken into account that drug bioavailability can be markedly modified by the presence of food in the gastrointestinal tract. Since food can modify the absorption rate of the active drug more than the prodrug, the bioavailability of a drug such as captopril has been reported to be reduced by 30%.[5] Food has no significant influence on the absorption of enalapril[6] or lisinopril.[7] Whether the concomitant use of drugs that modify the gastric pH has any effect on the amount of an orally administered ACE inhibitor that is absorbed, has not been systematically studied, but so far no clinically relevant interactions of this kind have been reported.

Metabolism: Many of the ACE inhibitors are prodrugs that are converted to the active drug during passage through the gastrointestinal mucosa and the liver.[8] Therefore, the bioavailability of these prodrugs, as well as the time for the active metabolite to reach its peak concentration, can be influenced by hepatic blood flow and the metabolic integrity of the hepatocytes. In a recent study that was undertaken to determine whether the presence of congestive heart failure (CHF) would alter the absorption, first-pass metabolism, and elimination of lisinopril and enalapril, it was reported that, although the serum concentrations of lisinopril were similar to those found in healthy subjects after single and multiple dosing, conversion of the prodrug enalapril to the active form enalaprilat appeared to be delayed and reduced in CHF patients and the time to and duration of the maximum concentration of enalaprilat was increased (see the article by Johnston and Duffin in this symposium). However, CHF has only minor effects on the plasma concentration–time profiles of lisinopril, enalapril, and enalaprilat, since decreases in gastrointestinal absorption and first-pass metabolism were balanced by reduced renal clearance.

The main step in the metabolism of the ACE inhibitors is their conversion from a prodrug to the active metabolite by esterases. Only captopril is extensively metabolized to disulfides, whereas a

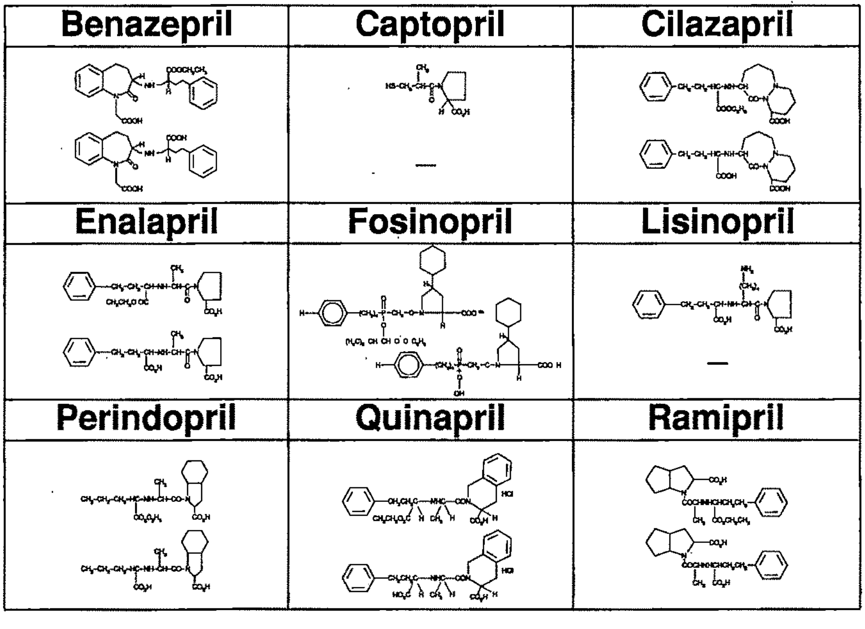

FIGURE 1. Chemical structure of some currently available angiotensin-converting enzyme inhibitors.

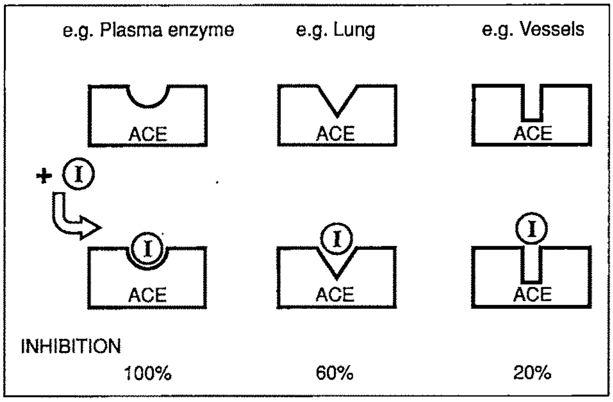

FIGURE 2. Cartoon representation of the active binding site of angiotensin-converting enzyme (ACE) from various tissues, showing that an inhibitor with a particular structure fits better in 1 enzyme than in another, resulting in varying degrees of ACE inhibition.

number of carboxyalkyl dipeptides are further transformed to diketopiperazines by a condensation reaction or to glucuronides by conjugation.[9] Although the bulk of deesterification occurs in the gastrointestinal mucosa and the liver, there are low levels of esterolytic enzymes in other tissues as well,[10] and there is a possibility that lipophilic prodrug molecules may penetrate the tissue and become deesterified to the more hydrophilic active ACE inhibitor. The presence or absence of these tissue esterases may contribute to the differences in tissue distribution and duration of action observed with some of the ACE inhibitors.

Distribution: Tissue availability of the ACE inhibitors, i.e., the concentration of the active drug near the enzyme, is determined by its lipophilicity, the relative lipid concentration of that particular tissue, and the presence of tissue esterases. However, tissue penetration by individual ACE inhibitors, and their possible metabolism by esterases, may not be solely responsible for this so-called relative tissue selectivity. The latter is apparently not only determined by differences in tissue bioavailability, but also by the relative affinity of different ACE inhibitors for ACE from different tissues. The affinity of the ACE inhibitor for a particular enzyme is not only determined by the structure of the inhibitor, but also by the structure of the enzyme. This means that, as illustrated in Figure 2, a particular ACE inhibitor will fit (and inhibit) more easily the active site of, e.g., the plasma enzyme than the active site of the enzyme in the lung or in the vessels. It has been suggested that the ACE enzymes from different tissues may be slightly different, varying with regard to their molecular weight, to the amino- and carboxyl-terminal amino acids in their structure and also to their degree of glycosylation.[11] Fabris et al,[12] by studying the displacement of a radiolabeled ligand by various ACE inhibitors in homogenates from different rat tissues, were able to show that the various molecules studied have different affinities for ACE from different tissues (Figure 3). From this figure, it is clear that a drug such as quinapril shows a different affinity for the ACE from the atria compared with that from the ventricles, whereas lisinopril and fosinopril appear to have a more consistent effect on the ACE from all tissues studied.

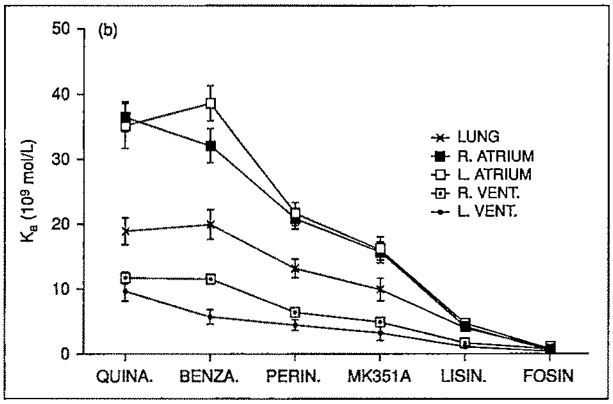

FIGURE 3. Equilibrium association constants for various angiotensin-converting enzyme (ACE) inhibitors with ACE from lung, right (R) and left (L) atrium, right and left ventricle (vent) from the rat. Competitive displacement experiments were performed by incubating the tissue homogenates with a radioligand inhibitor $[^{125}I]$351 A and increasing concentrations of 6 structurally different ACE inhibitors. (Adapted from *Clin Exp Pharmacol Physiol.*[12]) BENZA = benazepril; FOSIN = fosinopril; LISIN = lisinopril; PERIN = perindopril; QUINA = quinapril.

Elimination: The primary route of elimination of these drugs is the kidney, with the exception of ramiprilat and fosinoprilat, the latter being eliminated via urine and bile in nearly equal amounts.

Duration of inhibition by ACE, however, is not only determined by its clearance from the body via the kidney or the liver, but mainly by the affinity of the ACE inhibitor for a particular tissue enzyme and by the ease or difficulty with which the active ACE inhibitor is released from that tissue. It is clear that the higher the affinity of an inhibitor for the enzyme, the tighter it is bound, the longer it will stay in the tissue, and the longer its duration of action. This discrepancy between the rate of removal of the ACE inhibitor from the tissue compartment and the rate of removal from the plasma compartment results in an absence of a correlation between the duration of plasma versus tissue ACE inhibition and puts into question the value of determining the degree of plasma ACE inhibition by the various inhibitors in order to compare their duration of action.

PHARMACODYNAMICS

Affinity: The affinity of an ACE inhibitor, (i.e., the eagerness with which a drug will bind to its enzyme) is, among other things, a function of its structure. As shown in Figure 4A, it is clear that for an inhibitor that fits well in the active site of an enzyme, only a small amount of drug will be required to inhibit completely all the enzyme available in a particular tissue. Furthermore, the better the fit, the tighter the binding and the less tendency for release from the enzyme. On the other hand, as shown in Figure 4B, with an inhibitor with a different structure that does not fit as well in the active site, more of the drug will be required to inhibit a particular enzyme, and the drug is also more easily released from the active site. The higher the affinity of an ACE inhibitor for its enzyme, the less of the drug is required to inhibit the enzyme, and the higher is its potency. Fabris et al[13] compared the potency of various ACE inhibitors by measuring the displacement of a radiolabeled inhibitor from the plasma enzyme (Figure 5). From these experiments 2 important conclusions can be drawn. First, by increasing the concentration of the inhibitors studied, all of them are able to reduce the binding of the labeled substance to 0%, i.e., all substances can reach maximal efficacy, provided they are given in the corresponding dose. Secondly, since the dose–displacement curves show a difference in position of about 2 log units on the dose axis, 100 times less quinaprilat than captopril is required to obtain 50% displacement of the radiolabeled marker. In practice this means that, although less of a particular (potent) ACE inhibitor is required to obtain a

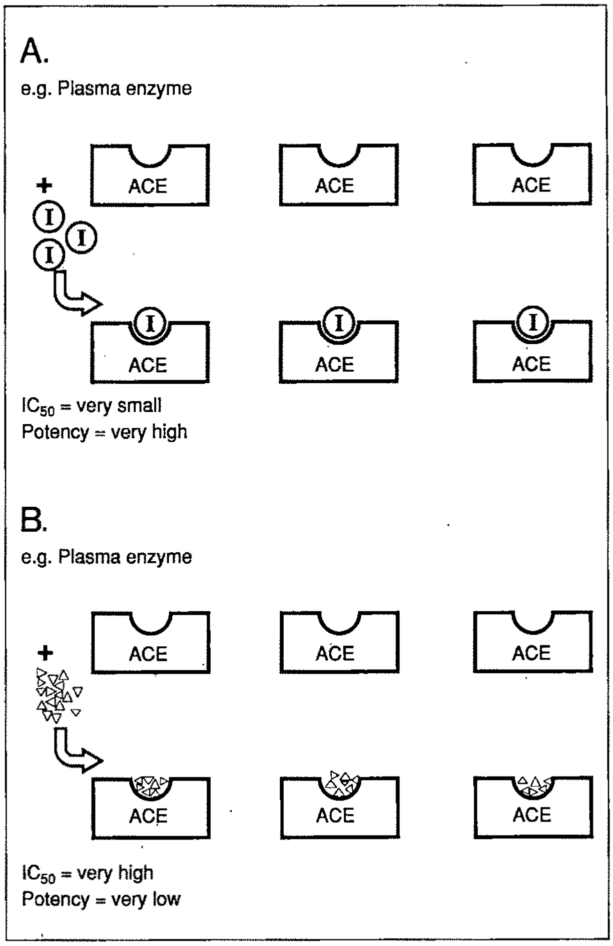

FIGURE 4. Cartoon representation of the interaction of a particular tissue angiotensin-converting enzyme (ACE), with ACE inhibitors with different structures. Of an ACE inhibitor whose structure fits well in the active site of the enzyme, only a small amount is required to inhibit the enzyme activity by 50% (IC$_{50}$ is very small; potency is very high) and the tendency to leave its nidus is less (*A*). Of an enzyme inhibitor whose structure does not fit as well in the active site, the opposite is true (*B*).

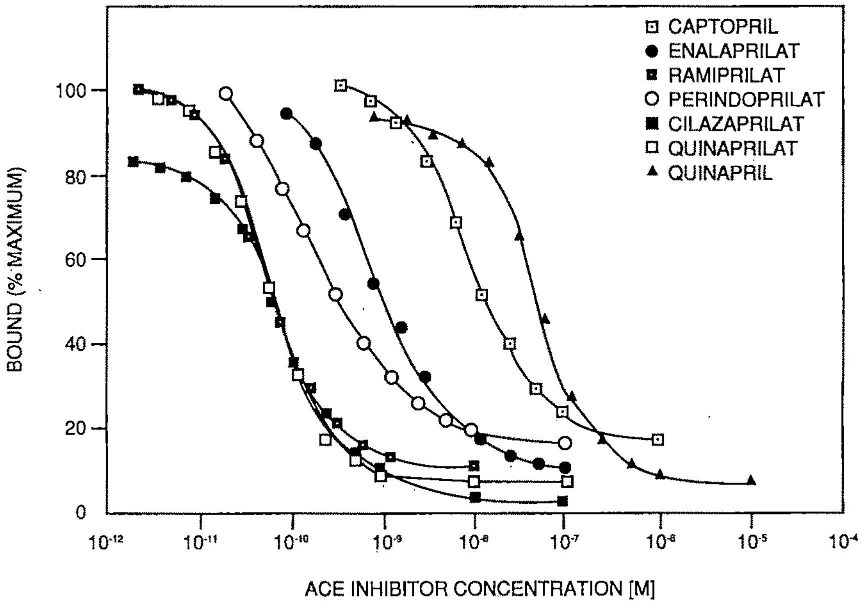

FIGURE 5. Binding displacement curves of radioligand inhibitor [^{125}I]351 A from human plasma angiotensin-converting enzyme (ACE) by various ACE inhibitors. (Adapted from *J Cardiovasc Pharmacol.*[13])

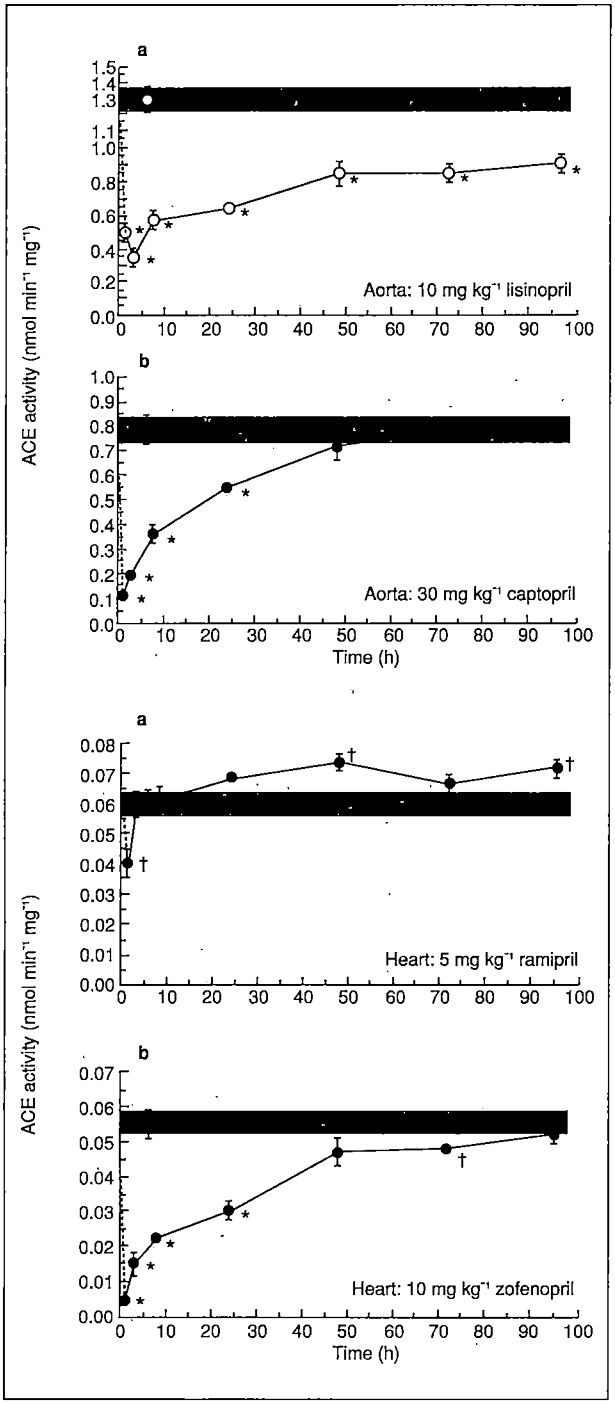

FIGURE 6. *TOP*: Activity of angiotensin-converting enzyme (ACE) in the aortae of spontaneously hypertensive rats (SHR) as a function of time following the administration of lisinopril at 10 mg/kg orally (*a*) and captopril at 30 mg/kg orally (*b*). ACE activity is shown as means ± standard error of the mean for tissues from 6 SHR. Statistical significance of values compared with those obtained from tissues from vehicle-treated controls (shaded bar) are indicated. *p <0.01. *BOTTOM*: Activity of ACE in SHR hearts as a function of time following the administration of ramipril at 5 mg/kg orally (*a*) and zofenopril at 10 mg/kg orally (*b*). ACE activity is shown as mean ± standard error of the mean for tissues from 6 SHR. Statistical significance of values compared with those obtained from tissues from vehicle-treated controls (shaded bar) are indicated. *p <0.01, $^{+}$p <0.05. (Adapted from *Br J Clin Pharmacol*.[14])

certain degree (e.g., 50%) of inhibition, all inhibitors, even a less potent drug, are able to inhibit the enzyme maximally, provided the dose can be sufficiently increased without the appearance of serious side effects.

As already mentioned, the higher the affinity of the drug, the tighter the binding of an ACE inhibitor to the enzyme and the longer it exerts its inhibitory activity. This is illustrated in Figure 6A and 6B[14] in which various ACE inhibitors were administered to spontaneously hypertensive rats in equihypotensive doses and, after different time intervals, the animals were killed and the remaining ACE activity in various organs was determined. Less of a substance such as lisinopril is required to produce inhibition of aortic ACE that lasts up to 100 hours after administration than is required of captopril which had completely disappeared 50 hours after the administration of a 3 times higher dose. Ramipril hardly inhibits the ACE in the heart, whereas an equihypotensive dose of zofenopril has a long-lasting inhibitory effect in this tissue, thereby illustrating again the "tissue selectivity" of some of the ACE inhibitors.

Presence of a sulfhydryl group: The immunologic side effects observed during the administration of high doses of captopril were initially ascribed to the presence of the sulfhydryl group in the molecule.[5] Later, when the use of smaller doses of captopril appeared to be devoid of these side effects[15] much attention was focused on the possible advantages of the sulfhydryl group. The presence of the latter in captopril has been shown to be responsible for the stimulation of the biosynthesis of vasodilating prostaglandins in renomedullary interstitial cells,[16] rat glomeruli[17] and rat aorta[18,19] and may contribute to the hypotensive effect of captopril. This stimulation of prostaglandin synthesis was not present in ACE inhibitors lacking the sulfhydryl group. However, this hypothesis has recently been challenged by Beierwaltes and Carretero[20] and by Hoffman et al,[21] who showed that the ability of ACE inhibitors to stimulate prostaglandin biosynthesis is not related to the sulfhydryl group, but to the prolonged survival of bradykinin. As shown in Figure 7, the increased production of prostacyclin, elicited by captopril or by lisinopril (which lacks the sulfhydryl group), was completely abolished in the presence of a bradykinin antagonist. A point of interest in these experiments was that the production of prostacyclin, in the presence of the bradykinin antagonist, fell below the levels of the controls, indicating that there might be a continuous basal production of bradykinin by the

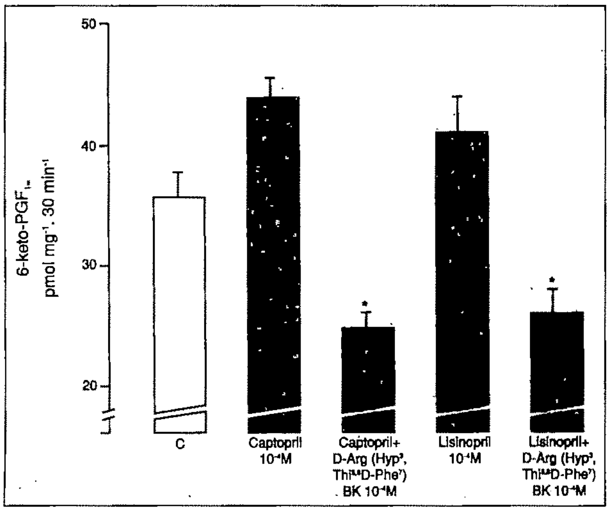

FIGURE 7. Effect of in vitro addition of the bradykinin antagonist D-Arg[Hyp^3, Thi^{5,8}, D-Phe^7]BK on lisinopril- and captopril-stimulated 6-keto-prostaglandin F$_{1\alpha}$(6-keto-PGF$_{1\alpha}$) synthesis by portions of isolated rat aorta. Each value represents the mean ± standard error of the mean of 8 incubations. C represents control incubations without the addition of either angiotensin-converting enzyme inhibitor or bradykinin antagonist. *$p < 0.01$ (compared with incubations containing 10^{-5} *M* lisinopril or captopril, respectively). (Adapted from *Eur J Pharmacol.*[21])

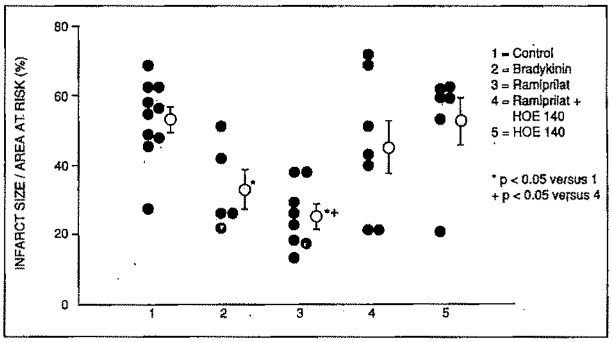

FIGURE 8. Infarct area, as percentage of the area at risk, in control dogs and in dogs treated with bradykinin, ramiprilat, ramiprilat plus the bradykinin antagonist HOE140, and HOE140 alone. Each filled circle represents 1 dog. Open circles are the mean ± standard error of the mean values. (Adapted from *Eur J Pharmacol.*[31])

endothelial cells, acting in an autocrine or paracrine fashion, as a potent stimulus for endothelial autacoid production. This hypothesis has recently been forwarded by Busse and Lamontagne[22] and by Wiemer et al[23] in relation to the ability of ACE inhibitors to stimulate the production of prostacyclin and endothelium-derived relaxing factor by cultured endothelial cells. The latter substance, initially described by Furchgott and Zawadzki,[24] has now been identified as nitric oxide.[25] It is synthesized from L-arginine by the nitric oxide-synthase and has potent vasodilating properties that play an important role in the regulation of the peripheral vascular tone.[26,27]

Protective effects against free radical–induced cell injury have been ascribed to the sulfhydryl-containing ACE inhibitors.[28] Although these substances undoubtedly have radical scavenging properties in vitro, very high concentrations are required, which might be difficult to obtain in vivo (for review see McMurray and Chopra[29]). Further, similarly to what was discussed previously about the possible involvement of bradykinin in some of the beneficial effects observed after ACE inhibition, recent experiments on reperfusion injury[30,31] in which a bradykinin antagonist was used, point in the same direction, i.e., reduction of the damage (infarct size, ischemia-induced arrhythmias) can be obtained by administration of either sulfhydryl- or nonsulfhydryl-containing ACE inhibitors and can be abolished by previous treatment of the animals with a selective bradykinin antagonist (Figure 8).

SIDE EFFECTS

The less selectively an ACE inhibitor is distributed in the organism, the more likely it is that side effects will occur as a result of the inhibition of ACE in tissues that are not "out of order" during the treatment of a particular disease. Furthermore, since the currently available ACE inhibitors are actually nonselective protease inhibitors and therefore also prevent the destruction of other peptides (e.g., enkephalins), side effects are not only the result of nontissue-specific inhibition, but also of non-ACE-related inhibition. Although the profile of the side effects observed after administration of the ACE inhibitors may vary, so far no data are available that any particular ACE inhibitor currently in use is devoid of the known side effects (cough, angioneurotic edema, modification of taste, etc.).

CONCLUSION

Although it may appear attractive to claim that a particular ACE inhibitor selectively inhibits ACE in one tissue more than in another, or that, due to the presence or absence of a sulfhydryl group or other modifications in its structure, the drug has been shown to have some special characteristics concerning endothelial autacoid production or tissue protective effects, none of these elements has so far been demonstrated to confer a specific benefit with the use of a particular drug. There are at present no data available to suggest that the ACE inhibitors currently being used in the treatment of CHF or hypertension differ in efficacy, or lack of side effects, because of their ability to inhibit ACE selectively in different tissues. Long-term follow-up of the existing or new ACE inhibitors might confirm or disprove the importance of selective tissue inhibition observed in the animal experiments.

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Drug–Patient Interactions and Their Relevance in the Treatment of Heart Failure

Dennis Johnston, PhD, MD, and Donal Duffin, MB, MRCP

The effects of congestive heart failure (CHF) on drug disposition and elimination are many and varied. Indeed, the pharmacokinetics of many of the drugs used to treat CHF are significantly altered by the patient's underlying condition. Reduced gastric emptying in CHF delays absorption and decreases the peak plasma concentrations of furosemide, bumetanide, and digoxin. Moreover, drugs that have a high hepatic extraction ratio (organic nitrates, morphine, prazosin, and hydralazine) achieve higher than expected plasma concentrations in patients with CHF. In contrast, drugs requiring biotransformation to active forms, e.g., angiotensin-converting enzyme (ACE) inhibitors such as enalapril, perindopril, quinapril, and ramipril, generally have lower than expected plasma concentrations. Nevertheless, ACE inhibitors can impair renal function in CHF, leading to an actual increase in plasma concentrations. However, decreases in absorption and first-pass metabolism are often offset by reduced hepatic and renal clearance. The overall absorption of lisinopril may be reduced in some CHF patients; consequently, the onset of effect is delayed but is often more prolonged.

(Am J Cardiol 1992;70:109C–112C)

Heart failure is a clinical condition in which the heart and circulation are unable to maintain the normal requirements of metabolizing tissue. The symptoms and signs experienced by patients with congestive heart failure (CHF) relate to reduced cardiac output and increased organ congestion. CHF causes pulmonary hypertension and elevated right heart filling pressures, which can cause hepatic and gastrointestinal congestion, In addition, reduced perfusion to the gut, liver, and kidney can alter drug handling in heart failure. In general these effects are unpredictable. Before discussing the effects of heart failure on drug disposition and elimination, it is necessary to define some basic pharmacokinetic terms.

BIOAVAILABILITY

The bioavailability of a drug is defined as the amount of drug that reaches the systemic circulation after administration. In most situations the term refers to oral bioavailability and is calculated as the ratio of the areas under the oral and intravenous concentration–time curves. Oral bioavailability is affected by drug interactions in the gut lumen, absorption through the gut wall, and by first-pass metabolism, which can occur in the gut wall or more frequently in the liver (Figure 1).

Absorption: Most absorption from the gastrointestinal tract takes place in the upper jejunum. The rate and amount absorbed are related to the physicochemical properties of the drug, blood flow, surface area of the absorbing surface, gastric emptying, and intestinal motility. Changes in the rate of gastric emptying alter drug delivery to the upper small intestine and the rate of absorption of lipid soluble drugs. In CHF gastric emptying tends to be reduced due to activation of the sympathetic nervous system or by opiates and drugs that have anticholinergic activity, such as antihistamines, class IA antiarrhythmic agents, and tricyclic antidepressants. This leads to delay in absorption and lower peak plasma concentrations. In addition, gut edema may partly explain malabsorption associated with CHF.[1] Absorption from muscle also

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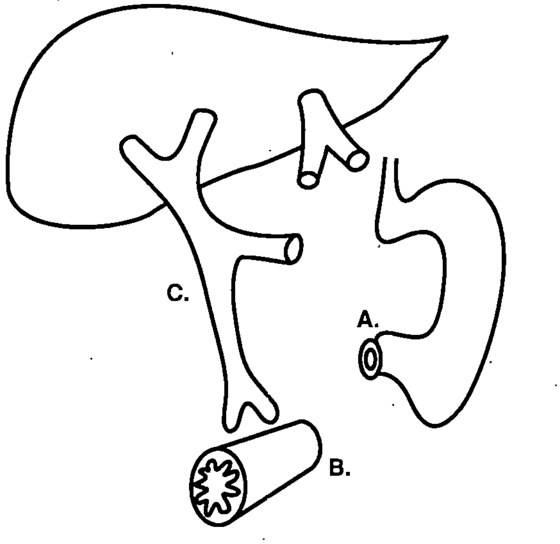
TABLE I First-Pass Metabolism in Heart Failure

Drugs	Degree of First-Pass Metabolism
Nitroglycerin	No accurate oral figures
Hydralazine	20–60%
Isosorbide dinitrate	20–60%
Lidocaine	30–50% oral
Morphine	20–30%; bioavailability
Prazosin	50–70%

depends on the physicochemical properties of the drug and muscle blood flow. Muscle blood flow is reduced in severe congestive cardiac failure, and the absorption of drugs that are poorly absorbed from muscle, including digoxin, quinidine, and diazepam, is further impaired.[2] Drugs that are soluble in interstitial fluid, e.g., streptomycin, appear to be more rapidly absorbed.[3]

First-pass metabolism: A substantial proportion of a drug may be metabolized after oral administration and so does not reach the systemic circulation. Chronic dosing with high extraction drugs produces higher steady-state concentrations than those predicted from single-dose studies due to saturation of first-pass metabolism. The clearance of drugs with high first-pass metabolism depends primarily on hepatic blood flow.[4] CHF can reduce first-pass metabolism. This results in higher concentrations of high extraction drugs and lower concentrations of agents that require hepatic metabolism to produce the active form. Examples of cardiac drugs that undergo extensive first-pass metabolism are listed in Table I.



A. Reduced gastric emptying
1. Increased sympathetic activity.
2. Drugs:- narcotic analgesics
drugs with anticholinergic activity.
B. Gut edema, reduced splanchnic blood flow and decreased intestinal motility.
C. First-pass metabolism.

FIGURE 1. Effects of heart failure on oral bioavailability.

Clearance through hepatic metabolism and renal excretion: Clearance is a measure of how rapidly drugs are eliminated from the body. It is calculated as the volume of plasma from which a drug is completely eliminated per unit of time. Most drugs are lipid soluble and must be converted to more water soluble compounds prior to excretion. In CHF there is a reduction in hepatic blood flow and increased venous congestion. Hepatic venous congestion can impair hepatic microsomal function and affect drugs with low extraction ratios, such as theophylline and warfarin. Although liver function tests are frequently abnormal in patients with heart failure,[5] these do not correlate with hepatic microsomal function.[6]

Renal excretion of drugs is determined by the glomerular filtration rate, plasma concentration, and molecular size of the compound. Renal clearance is the net result of filtration and active secretion or reabsorption in the tubules. Angiotensin II plays an important role in preserving renal function by maintaining efferent arterial tone in patients with severely impaired renal perfusion. In such patients converting enzyme inhibitors can cause marked deterioration in renal function. In most patients with CHF, however, azotemia is usually mild and well tolerated.[7] Glomerular filtration is usually reduced in heart failure and the elimination of renally cleared drugs is often impaired. Since hepatic blood flow and enzyme activity are more affected than renal function in heart failure, drug toxicity is more likely to occur with drugs that are metabolized in the liver than those eliminated by the kidney.[8]

Apparent volume of distribution: The apparent volume of distribution is a theoretical concept defined as the volume of plasma into which the drug dose would need to be distributed to achieve the measured plasma concentration. The volume of distribution therefore helps define the appropriate loading dose. One might expect that the volume of distribution would be increased in CHF.[6] However, fluid tends to be retained within the cells and is not in direct communication with the central compartment. On the contrary, the volume of distribution of several drugs is often reduced in heart failure; thus loading doses may need to be decreased (e.g., lidocaine).[8,9]

Elimination half-life: The elimination half-life is the time taken for the plasma concentration to

TABLE II Effects of Heart Failure on the Pharmacokinetics of Drugs Used for Its Management

Drug	Absorption	Metabolism	Renal Excretion
Furosemide Bumetanide	Reduced peak concentration and prolonged time to peak	—	Elimination half-life and renal clearance prolonged (related to renal function)
Digoxin	Reduced peak concentration and prolonged time to peak. Probably no overall effect	—	Related to the degree of renal impairment
Nitrates (oral dinitrate)	Unaffected	Higher plasma concentrations related to impaired first-pass metabolism	—
Hydralazine	Unaffected	Impaired hepatic metabolism. Longer $t_{1/2}(\times 2)$	—
Prazosin	Unaffected	Reduced first-pass metabolism. Longer $t_{1/2}$	

$t_{1/2}$ = elimination half-life.

TABLE III Effects of Heart Failure on the Pharmacokinetics of Some Angiotensin-Converting Enzyme Inhibitors

Drugs	Absorption	Metabolism	Renal Elimination
Captopril	—	—	Decrease related to secondary effects on renal function
Enalapril	—	Delayed formation of enalaprilat	Reduced excretion of enalaprilat due to reduced renal function
Lisinopril	Some delay with lower peaks	—	Reduced excretion with renal impairment
Cilazapril	—	Minor delay in conversion to cilazaprilat	Related to renal function

decrease by half. The elimination half-life is a measure of the rate of elimination and is proportional to the volume of distribution and inversely proportional to the clearance. For many drugs, the decrease in clearance is associated with a reduced volume of distribution, e.g., lidocaine, so that the elimination half-life may not be very different from that in healthy subjects.[10]

EFFECTS OF HEART FAILURE ON THE PHARMACOKINETICS OF DRUGS USED TO TREAT HEART FAILURE

Loop diuretics: Furosemide is associated with reduced peak plasma concentrations and a prolonged time to peak concentrations in patients with CHF (Table II). The total amount of furosemide absorbed, however, is unaffected.[11,12] The response of patients with CHF to furosemide appears blunted and may be related to reduced delivery of the drug to the tubules in this condition.[12] Similar findings have been described with bumetanide.[11]

Digoxin: As with loop diuretics, digoxin absorption is slower and peak concentrations are lower in patients with CHF compared with healthy control subjects.[13,14] The dose of digoxin should be reduced in the presence of renal impairment, but there is little evidence that heart failure alters the elimination half-life or renal clearance.[15] The dose of digoxin should be reduced in heart failure only if renal function is impaired (Table II).

Nitrates: The pharmacokinetics of nitroglycerin infusions have been studied in patients with CHF (Table II).[16] Some patients showed primary resistance or an attenuated response to nitroglycerin. This group had a lower total body clearance compared with normal responders, which could be explained by impaired hepatic metabolism secondary to venous congestion of the liver. The pharmacokinetics of isosorbide mononitrate and dinitrate appear to be unaffected by the presence of CHF, food, or hepatic disease.[17]

Hydralazine: In patients with CHF, absorption is unaltered after a single dose[18] but the elimination half-life is markedly prolonged (Table II). This may have been related to impaired hepatic metabolism associated with CHF, although Crawford and colleagues[19] were unable to demonstrate reduced clearance in patients with heart failure. The large intersubject variability seen with hydralazine in CHF can only be partly explained on the basis of alterations in pharmacokinetics.

Prazosin: The time to peak concentration is not significantly altered in patients with heart failure (Table II). The area under the concentration–time curve is greater in patients with CHF than healthy volunteers, possibly due to impaired clearance.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The effects of converting enzyme inhibition on renal function is variable (Table III). Renal plasma flow is usually unchanged or slightly increased, whereas the glomerular filtration rate may decrease, particularly in patients with CHF.[20] Impairment of renal function tends to occur when renal perfusion is reduced.[21]

Captopril: Changes in the pharmacokinetics of captopril in heart failure are related to secondary renal dysfunction. Deterioration in renal function may occur during chronic therapy due to the attenuation of angiotensin II–mediated vasoconstriction of the efferent glomerular arterioles that maintain glomerular filtration.[7]

Enalapril: Enalapril is a prodrug requiring biotransformation to yield the active diacid inhibitor enalaprilat. The bioavailability of enalaprilat is reduced in CHF due to a reduction in the rate of absorption and decreased hydrolysis. Peak plasma concentrations and onset of clinical effect, therefore, tend to be delayed.[22] Both enalapril and enalaprilat are excreted primarily in the urine, and plasma concentrations tend to be higher in the presence of renal impairment.

Lisinopril: Lisinopril is the lysine analog of enalaprilat, the active metabolite of enalapril. It is active after oral administration and does not require biotransformation to induce pharmacologic effects. Compared with healthy volunteers, absorption in patients with heart failure is reduced,[23] but plasma concentrations are higher, suggesting a reduced volume of distribution. As a result, the onset of action is delayed, but more prolonged.[24]

CONCLUSIONS

Reduced gastric emptying occurring in CHF can prolong drug absorption and reduce the peak plasma concentrations of the loop diuretics furosemide, bumetanide, and digoxin. Gut edema, reduced splanchnic blood flow, and decreased intestinal motility can reduce overall absorption. This is seen with the angiotensin-converting enzyme (ACE) inhibitor lisinopril in some studies. Drugs that have a high hepatic extraction ratio achieve higher concentrations in heart failure due to reduced first-pass metabolism. Examples include organic nitrates, morphine, prazosin and hydralazine. In contrast, drugs that undergo biotransformation in the liver to their active form will generally have lower plasma concentrations. The ACE inhibitors enalaprilat, perindoprilat, quinaprilat, and ramiprilat are prime examples of the latter effect. Plasma elimination half-lives are frequently prolonged as a result of impaired hepatic metabolism (e.g., prazosin, hydralazine) or secondary to reductions in renal function (furosemide, bumetanide, digoxin, and most ACE inhibitors). In CHF, ACE inhibitors can further impair renal function and plasma levels may increase. In general, however, decreases in absorption and first-pass metabolism are compensated for by a reduction in hepatic and renal clearance.

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Angiotensin-Converting Enzyme Inhibition, the Sympathetic Nervous System, and Congestive Heart Failure

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Catecholamines have been found to be powerful indicators of prognosis in patients with congestive heart failure. However, it is uncertain whether catecholamines are a marker for decreased cardiac performance or part of the pathologic process. Catecholamines, exogenously derived β-adrenergic stimulants, and drugs that amplify sympathetic responsiveness produce early hemodynamic benefits, but do not appear to provide long-term improvement in terms of symptoms or exercise tolerance, whereas blockade of the β-adrenoceptor appears to have little early benefit but may improve long-term prognosis. This suggests that in the long term, increased catecholamine levels may be deleterious. Angiotensin-converting enzyme (ACE) inhibitors can modulate circulating catecholamines, and the persistence and degree of ACE inhibition may be important not only in reducing catecholamines, but possibly also in reducing mortality in heart failure. It appears that ACE inhibitors definitely reduce mortality in congestive heart failure. It remains to be documented whether the persistence and degree of ACE inhibition is a factor in this effect, and, thus, comparison of short- with long-acting ACE inhibitors and study of the dosage of ACE inhibitors are of importance. The extent to which modulation of the sympathetic nervous system by ACE inhibitors is an important mechanism in their effect in reducing mortality remains to be established.

(Am J Cardiol 1992;70:113C–118C)

The sympathetic nervous system and its modulation represents one of the major noncardiac compensatory mechanisms that the body mobilizes in the presence of reduced cardiac output in congestive heart failure (CHF).[1] Several questions arise when presented with the rational treatment of heart failure:

1. Are the changes in the sympathetic nervous system necessary to the maintenance of cardiovascular homeostasis in the patient?
2. Are they beneficial or detrimental in the short term?
3. Are they beneficial or detrimental in the long term?
4. Is therapeutic intervention aimed at reducing sympathetic nervous system activation a worthwhile or practicable target?

THE SYMPATHETIC NERVOUS SYSTEM AND HEART FAILURE

Any decline in cardiac function that results in a decrease in central blood pressure is rapidly detected by the baroreceptors, which in turn reactively increase sympathetic tone via the central nervous system.[2] If subsequent sympathetic nervous system–mediated vasoconstriction and increased cardiac output fail to achieve the desired blood pressure, activation of the baroreceptor function may continue unchecked, encouraging in turn, further neurohormonal activation,[3] baroreceptor dysfunction,[4] and a hyperadrenergic state. In many ways, this upwardly spiralling cycle of increasing adrenergic tone reflects the downwardly spiralling myocardial function of CHF. The inverse relation between the cardiac function and sympathetic tone is well documented, and in patients with CHF, plasma norepinephrine levels are increased in proportion to the clinical severity of the disease.[5]

It remains to be established whether this increased sympathetic activity merely reflects the deterioration of cardiac function, or whether it is

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contributory to the decline in cardiac performance. Early in CHF, when cardiac output is limited only by exercise, plasma epinephrine and norepinephrine concentrations reflect this, being normal at rest and increasing abnormally on exertion.[6,7] Cardiac output becomes progressively reduced at rest as the heart failure syndrome increases in severity. As a result, catecholamines become elevated at rest and their elevation on exercise closely reflects the severity of functional and hemodynamic impairment.[5,8] Increased sympathetic tone may be evident before activation of the renin–angiotensin–aldosterone system (RAAS). Increased sympathetic tone may also be reflected in down-regulation of adrenergic receptors in heart failure.[9,10]

SYMPATHETIC NERVOUS SYSTEM ACTIVATION IN HEART FAILURE—GOOD OR BAD?

Perhaps clues to the answer to this question can be gleaned from reflecting on the effects of various drugs on heart failure and sympathetic activity. Treatment with β_1-selective or β_2-selective adrenoceptor agonists has failed to improve exercise capacity or symptoms in double-blind, placebo-controlled trials.[11–13] Nevertheless, these agents undoubtedly have early and apparently beneficial hemodynamic effects when used in the short term, but prolonged use results in a further reduction of β-receptor sensitivity and a reduction in hemodynamic effectiveness.[14] Additional risks of adrenergic stimulation are increased myocardial ischemia and arrhythmogenesis.[15,16] If β receptor down-regulation is a self-protecting mechanism used to limit "overenthusiasm" by the sympathetic nervous system, then blockade of the adrenergic/sympathetic nervous systems should produce beneficial effects.

Long-term treatment with low doses (6.25–100 mg daily, average) of the β blocker metoprolol in carefully selected patients (with CHF resulting from cardiomyopathy with normal coronary angiograms and stable compensated heart failure)[17–19] produced evidence of improved left ventricular function and symptoms in congestive cardiomyopathy. Greatest improvement was seen in those with the poorest ejection fractions and highest heart rates prior to treatment, and presumably those patients also had the highest catecholamine levels (vide supra).[20]

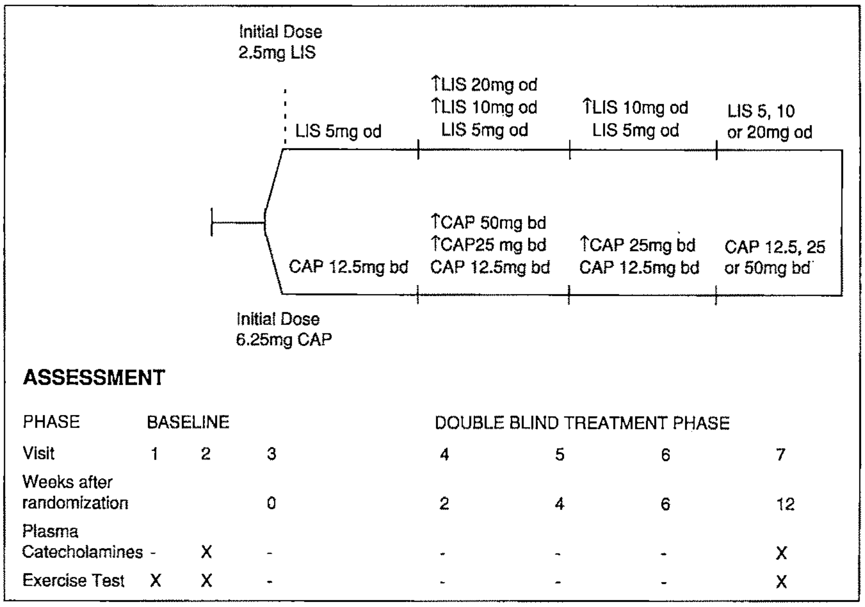
The use of β stimulants has been associated with high rates of mortality in heart failure patients,[21,22] as have phosphodiesterase inhibitors, (drugs that enhance levels of cyclic adenosine monophosphate, the intracellular messenger of adrenergic stimulation in cardiac tissue).[23] These findings come from relatively long-term use; these contrast with the observation of much improved hemodynamics when these drugs are used for short periods (4–8 weeks).[24] It has been established for some years that long-term (>6 months) β blockade increases β-receptor density and responsiveness to adrenergic stimulation.[25,26] Just as the early hemodynamic benefits seen with β-adrenergic stimulants do not seem to be translated into long-term beneficial effects, so acute treatment (<48 hours) with β blockers does not appear to be associated with benefit,[27,28] although longer term treatment is.[17–20]

Blockade of peripheral α_1 receptors produces vasodilation and some short-term benefit,[29,30] but in the long term, little benefit can be demonstrated.[31,32] Indeed, prazosin has been shown to have a less beneficial effect on mortality than combined hydralazine and nitrate therapy,[33] and this latter treatment has, in turn, been shown to be less effective than the angiotensin-converting enzyme (ACE) inhibitor enalapril.[34] Patients with the highest plasma norepinephrine levels in CHF have the worst prognosis,[35,36] but we must not leap to a conclusion as to cause and effect, for the former may be a marker for the severity of the heart failure, and may not directly be part of the underlying pathologic condition. Nevertheless, increased circulating catecholamines provide some element of measurement of risk, which may be independent of hemodynamic variables.[35,37]

Overall, observations on the behavior of the adrenergic system in CHF, and of the effects of drugs that promote or obtund its activity, suggest that, although clinical benefit can result from increased activity of the sympathetic nervous system in the short term, its long- term effects may be deleterious.

ACE INHIBITION AND SYMPATHETIC TONE

The use of ACE inhibitors such as enalapril in CHF has been shown to be associated with reduced mortality.[38,39] Although their action in blocking the unwanted vasoconstriction and salt- and water-retaining activities of the RAAS are probably paramount among the reasons for their effectiveness, there remains, nevertheless, the possibility that they have other actions. ACE inhibitors produce a decrease in systemic pressure without increasing heart rate and have been observed to reduce the circulating catecholamine concentrations and to restore sympathetic responsiveness by β-receptor up-regulation.[40,41] The absence of reflex



ASSESSMENT

PHASE	BASELINE			DOUBLE BLIND TREATMENT PHASE			
Visit	1	2	3	4	5	6	7
Weeks after randomization			0	2	4	6	12
Plasma Catecholamines	-	X	-	-	-	-	X
Exercise Test	X	X	-	-	-	-	X

FIGURE 1. Schematic representation of study design. bd = twice daily; CAP = captopril; LIS = lisinopril; od = daily; ↑ = dose could be increased at this visit if necessary.

tachycardia in the presence of vasodilation and the up-regulation of β receptors suggests that ACE inhibitors may have a small but possibly important effect on resting sympathetic tone,[42,43] possibly by modulating baroreceptor function,[44] although these effects could also be explained by increased parasympathetic activity.[45]

We have recently concluded a small-scale study to examine the effects of short- and long-acting ACE inhibitors captopril and lisinopril on catecholamine levels in patients with CHF. The study was a randomized, double-blind, parallel-group design, which compared lisinopril 5–20 mg once daily with twice-daily captopril 12.5–50 mg in patients with CHF (grades II or III on the New York Heart Association classification) (Figure 1). Patients were maintained on optimal doses of digoxin and diuretics throughout the study. There were 102 patients in the study, 11 withdrawing during the single-blind, placebo run-in period. After the run-in period, 47 patients were randomized to receive lisinopril and 44 patients to receive captopril. The randomized treatment period was 12 weeks. The treatment dose was increased after 2 or 4 weeks if significant signs and symptoms of heart failure indicated that an additional therapeutic effect was required, or if the physician thought that further treatment was justified, providing that standing systolic blood pressure was ≥90 mm Hg and that no symptoms of hypotension had been observed on the previous dose. The primary endpoint of this study was to detect any difference between the effect of lisinopril or captopril treatments on catecholamine levels (norepinephrine and epinephrine). A secondary endpoint was exercise duration.

Plasma norepinephrine concentrations increased over 12 weeks of captopril treatment by 59.2 pg/mL, compared with a net decrease on lisinopril treatment of 24.7 pg/mL. The estimated difference between these 2 treatment effects was −83.9 pg/mL (95% confidence interval −179.0 to +11.2 pg/mL). This difference approached statistical significance ($p = 0.0829$; Figure 2). There was no evidence of any statistical difference between the 2 treatments with regard to their effect on epinephrine levels over the 12-week study period. Epinephrine levels increased slightly on captopril treatment by 0.25 pg/mL, compared with a slight decrease on lisinopril treatment of 0.03 pg/mL (Figure 3).

Both captopril and lisinopril treatments produced significant increases in exercise duration from run-in. Captopril increased exercise duration

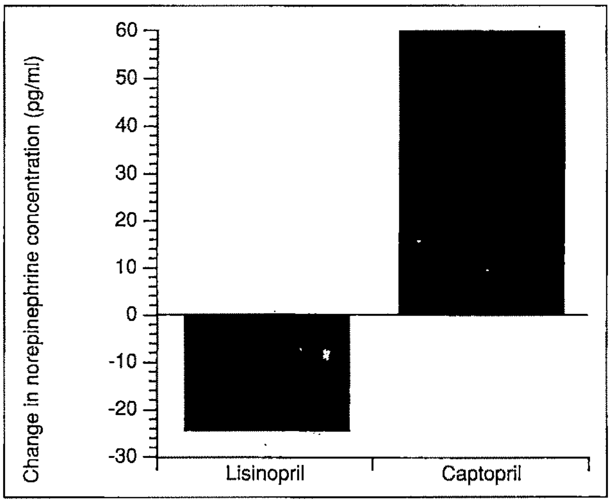


FIGURE 2. Changes in plasma norepinephrine concentrations (least squares means) after 12 weeks of treatment with lisinopril or captopril.

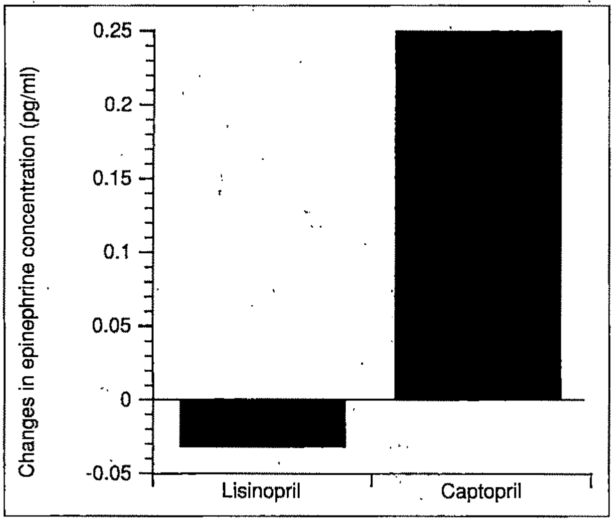


FIGURE 3. Changes in plasma epinephrine concentrations (least squares means) after 12 weeks of treatment with lisinopril or captopril.

by 73.7 seconds (p = 0.0055) and lisinopril increased exercise duration by 97.7 seconds (p = 0.0004; Figure 4).

One patient died suddenly 11 days after commencing randomized treatment (captopril). An autopsy was not performed. Including this patient, 3 out of 47 patients (6.4%) who received lisinopril and 4 of 44 patients (9.1%) who received captopril withdrew from the study due to adverse events. No significant difference was detected between the treatment groups (p = 0.7080). Events leading to withdrawal in both groups are summarized in Table I.

DISCUSSION

Previous studies with a variety of ACE inhibitors have suggested that ACE inhibition may reduce sympathetic nervous system activity.[42–44] The mechanisms by which this may be achieved has been partly attributed to a reduction in angiotensin II mediated norepinephrine release from nerve endings,[42–44] and a reduction in norepinephrine release from heart tissue has been shown with lisinopril previously.[43] It is tempting to postulate that suppression of the activity of the sympathetic nervous system is one of the mechanisms through which ACE inhibitors might achieve their reduction in mortality in CHF. However, more research is required to address this situation fully.

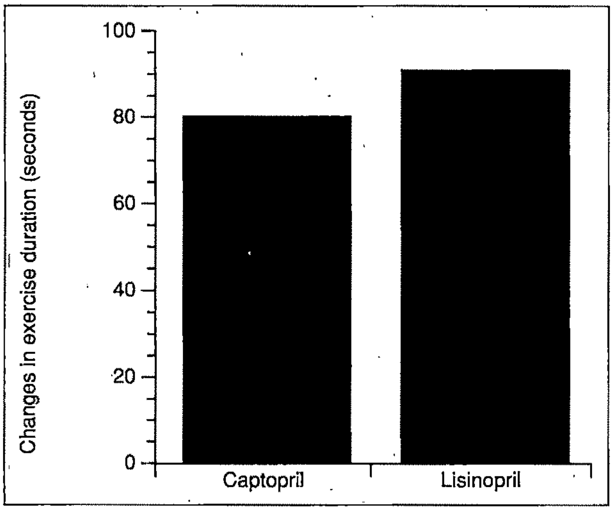


FIGURE 4. Mean changes in exercise duration from run-in after 12 weeks of treatment with lisinopril or captopril.

TABLE I Adverse Events Leading to Withdrawal from Randomized Treatment (Excluding Deaths)

Treatment at Onset	Reason	Relation to Study Medication (Investigator's Opinion)
Lisinopril	Left ventricular function	Unlikely
Lisinopril	Polydipsia Taste unusual Anorexia Constipation Gastric distensiondysuria Nausea	Probable
Lisinopril	Headaches Dizziness Nausea Coughing Dyspnea	Possible
Captopril	Congestive cardiac failure	Unlikely
Captopril	Cardiac failure Increased liver function test results Renal impairment	Possible
Captopril	Light headedness Decrease in blood pressure	Probable
Captopril	Nausea Hunger Lethargy Flushes and hot sweats Loss of taste	Probable

Those studies that have demonstrated a reduction in mortality with ACE inhibitors have all used relatively high doses, (e.g., enalapril 20–40 mg/day), and there are now reports emerging suggesting a possible dose–effect relationship in CHF with ACE inhibitors, both in terms of hemodynamics (e.g., quinapril 5–20 mg twice daily)[46] and mortality (e.g., enalapril 2.5 or 15 mg twice daily),[47] with greatest benefit being demonstrated for the highest doses. The duration of ACE inhibition is dose related[48] and partially dependent on the pharmacokinetic half-life of the particular drug used.[49]

Our findings of a difference, albeit small, in the effects of lisinopril and captopril on norepinephrine release could be partly explained by the pharmacokinetics and duration of action of the 2 drugs. An increase in plasma norepinephrine concentrations on captopril and a trend toward a decrease in plasma norepinephrine with lisinopril may reflect the persistence and degree of ACE inhibition achieved with the 2 drugs. Lisinopril has a relatively long plasma half-life of 12.6 hours compared with that of captopril (1.9 hours).[50,51] Moreover, it is possible that a more sustained ACE inhibition, and thereby suppression of angiotensin II–facilitated norepinephrine release, was achieved by lisinopril than by captopril.

Packer[52] has suggested that it may take as long as 12 weeks of treatment to separate placebo- from active drug-related effects and that the true effects of treatment may not be fully apparent until after 3–6 months continuous therapy. Since the early part of this study involved dose titration, it is possible that the study was of insufficient duration at the optimum dose of both lisinopril and captopril for treatment-related effects to become fully apparent. Hence, only a trend toward a treatment difference was apparent. Additional problems exist with this study: firstly, the difficulty of plasma catecholamine assays and, secondly, the sensitivity of the study to detect small differences between treatments. Previous studies comparing captopril with placebo and lisinopril with placebo suggest that changes in circulating catecholamine levels are in the range of 100–500 pg/mL.[43,53] This present study could have detected a difference between treatments of 1 nmol/liter (167.2 pg/mL) in norepinephrine levels. The clinical relevance of such changes remains to be established.

CONCLUSION

If, indeed, increased sympathetic nervous system activity is a contributory factor in the decline in cardiac function and mortality in heart failure, then treatment with ACE inhibitors should aim at suppressing as completely as possible the effect of the RAAS on the action of the sympathetic nervous system. Clearly, more work is required to elucidate the mechanisms by which ACE inhibitors achieve their beneficial effects in heart failure and to explore the relative importance of their influence on the sympathetic nervous system in this.

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Angiotensin-Converting Enzyme Inhibitors and Renal Function in Heart Failure

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Patients with severe heart failure often exhibit signs of an impaired renal function. As judged from serum urea and creatinine concentrations, renal function may deteriorate further after the addition of angiotensin-converting enzyme (ACE) inhibitors to therapy. The beneficial effect of unloading the failing heart by reducing the systemic outflow resistance is opposed by a potentially harmful effect of unloading the kidney by preferentially reducing the outflow resistance of the glomerulus. However, development of functional renal insufficiency is unlikely and is a rare cause for withdrawing ACE inhibitors when certain precautions are considered: (1) The initial dose of the ACE inhibitor has to be reduced with increasing severity of heart failure (the titration period thereafter should be monitored carefully); (2) an increase in serum creatinine not exceeding 30% of the basal value may be taken as evidence for a beneficial action of the drug, which in addition to altering cardiac function alters kidney function (when the increase in serum creatinine is considered to be of clinical significance, it seems wise to reduce the dose of diuretics first—thereby neuroendocrine stimulation can be attenuated and the dependency of renal filtration from angiotensin II–induced efferent vasoconstriction can be reduced); and (3) the coadministration of inhibitors of prostaglandin synthesis (e.g., acetylsalicylic acid) appears to be associated with a higher risk of impairing renal function: the decrease in glomerular filtration rate is more marked and the compensatory increase in renal plasma flow following ACE inhibition is no longer observed.

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In patients with severe heart failure the renin–angiotensin system is intimately linked to the maintenance of renal function.[1,2] Angiotensin II–mediated vasoconstriction in the systemic circulation[3] helps to keep renal perfusion pressure above the threshold of autoregulation. Intrarenal actions of angiotensin II help to adjust intraglomerular pressure in order to maintain glomerular filtration.

Blockade of the renin–angiotensin system in severe heart failure patients may, therefore, interfere critcally with the homeostatic mechanisms for renal excretion. From a retrospective analysis various factors have been found that may predict the probability of inducing functional renal insufficiency by angiotensin-converting enzyme (ACE) inhibition in congestive heart failure (CHF) patients.

Both the presence of hyponatremia and the dose of diuretics have been identified as prognostic factors of worsening renal function.[4] A reduced serum sodium concentration and/or high doses of diuretics in patients with CHF are in general associated with a highly stimulated renin–angiotensin system. Under these circumstances, blockade of the system may result not only in unloading of the heart,[5] but also in "unloading" of the kidney, ultimately resulting in cessation of excretion.

Not only the degree of blockade of renin–angiotensin system but also the duration of blockade during a 24-hour cycle may matter for renal function. The observation that the long-acting ACE inhibitor enalapril induced more marked changes in renal function than the short-acting captopril[6,7] led to the assumption that long-acting ACE inhibitors should be regarded as an additional risk factor for functional renal insufficiency. However, the policy of introducing ACE inhibitors into the regimen of treatment of severe heart failure has changed since then. Instead of large fixed doses of long-acting substances, without adjusting the dose of diuretics, patients with severe heart failure generally receive low doses of ACE inhibitors at the beginning, with dosage titrated

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TABLE I Patient Demographics

	Captopril	Lisinopril
Age (yr)	55.8 ± 3.9	61.8 ± 2.5
Sex (M/F)	7/3	10/1
Body weight (kg)	70.5 ± 2.7	85.7 ± 3.9
Height (cm)	170.7 ± 2.9	172.0 ± 2.6
Etiology		
Ischemic heart disease	6	4
Dilated cardiomyopathy	4	7

TABLE II Starting Dose and Titration Steps for Captopril and Lisinopril in Heart Failure Patients

	Day				
Drug	1	2	3	4	5
Captopril (mg)	1 × 6.25	2 × 12.5	3 × 12.5	3 × 12.5	3 × 12.5
Lisinopril (mg)	1 × 2.50	1 × 5.0	1 × 10.0	1 × 10.0	1 × 10.0

thereafter. The doses of diuretics are then adjusted to the needs of the patients. Whether administration of long-acting ACE inhibitors would still bear a higher risk of inducing functional renal insufficiency under these more clinically relevant conditions remains unclear.

MATERIALS AND METHODS

Patients: Detailed analysis of renal function was performed in 21 patients with CHF in New York Heart Association (NYHA) functional classes II–III. The underlying heart disease was confirmed by left and right heart catheterization and was found to be ischemic heart disease in 10 patients and dilated cardiomyopathy in the remaining 11 patients. The demographic data showed no major differences between patients allocated to captopril or lisinopril treatment (Table I), with the exception of body weight. During an initial stabilization period, the dosage of diuretics was adjusted and kept constant throughout the investigation period. Administration of digitalis and vasodilators (except ACE inhibitors) was continued at the same dosages as those used during the preinvestigation period.

Measurements of renal function and 24-hour ambulatory blood pressure recordings were performed on the day before (day 0) and 5 days (day 5) following the initiation of ACE inhibitor therapy. The dose-titration schedules used for both captopril (n = 10) and lisinopril (n = 11) are shown in Table II.

Measurement of blood pressure and heart rate: Ambulatory blood pressure and heart rate were recorded (Spacelabs monitors 90202–02 or 90207–32); during daytime (from 8 AM to 10 PM), readings were taken every 20 minutes, but only every 60 minutes during the night. During the 3-hour period of measuring renal function additional readings were performed every 10 minutes to detect deviations of blood pressure of shorter duration.

Measurement of renal function: Creatinine clearance is not a reliable marker of glomerular filtration in heart failure with reduced renal function.[8] Collection of 24-hour urine is hampered in patients with heart failure by incompleteness of sampling. Thus, glomerular filtration rate was calculated from inulin clearance and renal plasma flow from *para*-aminohippuric acid (PAH) clearance. Inulin (1,500 mg/m^2 body surface area) and PAH (500 mg/m^2) were initially administered as a bolus dose, which was followed by a continuous infusion (inulin 10 mg/min/m^2; PAH 8 mg/min/m^2) for 3 hours. Steady-state conditions were achieved 90 minutes after the beginning of the infusion and venous blood samples were taken every 15 minutes thereafter for determinations of inulin and PAH concentrations. On day 5, captopril and lisinopril were given 1 hour and 4 hours, respectively, prior to the assessment of renal function.

RESULTS

Heart rate and blood pressure: During the 3-hour period of measurement of renal function, mean heart rate decreased by 4–5 beats/min following administration of captopril and lisinopril. Mean arterial blood pressure was significantly reduced on day 5 by both captopril (−13 mm Hg) and lisinopril (−10 mm Hg) compared with baseline. There were no episodes of symptomatic hypotension in either treatment group. In addition, there were no significant differences between the ACE inhibitors with respect to their effects on heart rate and blood pressure during the time of determining renal function.

Serum electrolytes, urea, and creatinine: Serum sodium and potassium concentrations remained virtually unchanged during the initial phase of treatment with both ACE inhibitors (Table III) and did not change significantly during the first 5 days of ACE inhibitor treatment. Only 1 patient in each group experienced an increase in serum creatinine ≥0.4 mg/dL (captopril from 1.2 to 1.9 mg/dL, lisinopril from 1.4 to 1.8 mg/dL).

Inulin and PAH clearances: In both groups, glomerular filtration rate (inulin clearance) decreased (captopril from 104.6 ± 8.8 to 100.2 ± 7.3 mL/min), but it reached significance only in the patients treated with lisinopril (from 105.3 ± 6.2 to 97.5 ± 4.9 mL/min, decrease = 7.8 mL/min; $p < 0.05$). There was a concomitant, but not statistically significant increase in renal plasma flow (PAH clearance) from 414.3 ± 46.5 to 434.9 ± 37.5 mL/min for captopril and from 371.9 ± 29.0 to 399.5 ± 31.5 mL/min for lisinopril. Hence, filtration fraction consistently decreased following ACE inhibition (captopril: from 0.263 ± 0.022 to 0.239 ± 0.021 mL/min, $p < 0.05$; lisinopril: from 0.293 ± 0.018 to 0.257 ± 0.021 mL/min, $p < 0.05$). Thus, changes in renal function predictably occurred with the induction of ACE inhibitor therapy. No differences were observed between the alterations induced by the short-acting ACE inhibitor captopril compared with the long-acting ACE inhibitor lisinopril.

Relations between hemodynamics and renal function: The following linear relations between hemodynamics and renal function could be detected: (1) a significant positive correlation between the mean arterial blood pressure on day 5 and glomerular filtration rate on day 5 (glomerular filtration rate = 0.49 × mean arterial blood pressure + 53.1; $r = 0.69$; $p < 0.001$; $n = 31$); and (2) a significant inverse correlation between mean arterial blood pressure on day 5 and renal plasma flow on day 5 (renal plasma flow = −2.31 × mean arterial blood pressure + 584.5; $r = -0.65$; $p < 0.001$; $n = 31$).

No significant correlations could be detected between: (1) the change in mean arterial blood pressure (day 0 to day 5) versus the change in glomerular filtration rate; (2) the absolute values for mean arterial blood pressure on day 0 versus glomerular filtration rate on day 0; (3) the change in mean arterial blood pressure (or absolute values on day 0) versus renal plasma flow; and (4) the change in mean arterial blood pressure (or absolute values on day 5) versus changes in filtration fraction or changes in renal resistance.

Influence of acetylsalicylic acid: In a retrospective analysis, a comparison was made between the changes observed in renal function obtained from 10 patients who received acetylsalicylic acid (100–1,000 mg/day) in addition to the ACE inhibitor compared with 21 patients receiving only ACE inhibitors without addition of acetylsalicylic acid. Figure 1 shows the changes in glomerular filtration rate and renal plasma flow in both groups. The coadministration of acetylsalicylic acid with ACE inhibitors in heart failure patients led to a marked change in the pattern of renal function alterations due to ACE inhibition: the decrease in glomerular filtration rate was more marked (−9% vs −5%) but the increase in renal plasma flow was attenuated (2.5% vs 17%; Figure 1). Accordingly, renal blood flow was not enhanced further (0.4% vs 11%) and the reduction of renal resistance was impaired (−5.5% instead of −8.5%).

TABLE III Changes in Serum Sodium, Potassium, Urea, and Creatinine After 5 Days of Treatment with Captopril or Lisinopril

	Day	Captopril	Lisinopril
Na^+ (mmol/liter)	0	137.9 ± 0.7	137.7 ± 0.8
	5	137.2 ± 1.1	134.7 ± 1.2
K^+ (mmol/liter)	0	4.1 ± 0.1	4.3 ± 0.2
	5	4.2 ± 0.1	4.3 ± 0.1
Urea (mg/dL)	0	35.9 ± 4.6	44.1 ± 7.0
	5	39.6 ± 5.6	49.4 ± 8.5
Creatinine (mg/dL)	0	1.1 ± 0.1	1.2 ± 0.1
	5	1.1 ± 0.1	1.2 ± 0.1

Na^+ = sodium ion; K^+ = potassium ion.

DISCUSSION

The kidney in heart failure: The reduction of stroke volume, the decrease in blood pressure, and the activation of vasopressor systems contribute to alteration of kidney function in heart failure (Figure 2). Among the vasopressor systems activated in heart failure, the renin–angiotensin system plays a key role in affecting the systemic circulation as well as the renal circulation.

The stimulated activity of the renin–angiotensin system in heart failure has long been considered to be a compensatory mechanism, counteracting critical decreases in blood pressure and maintaining renal excretory function. Although the concept of "compensation" for the systemic circulation can no longer be held, because of the detrimental effects of an increased afterload on the failing heart, the

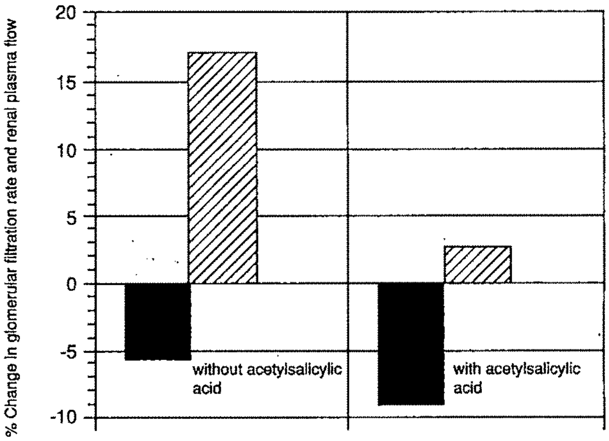

FIGURE 1. **Changes in glomerular filtration rate (*filled bars*) and renal plasma flow (*hatched bars*) in 21 patients receiving angiotensin–converting enzyme (ACE) inhibitors and in 10 patients who also received acetylsalicylic acid.**

“beneficial” effects of angiotensin II on the kidney are still a matter of debate.

Angiotensin II increases efferent arteriolar resistance to a greater degree than afferent resistance.[9] In heart failure, the resulting increase in intraglomerular pressure helps to maintain filtration fraction. The angiotensin II–induced stimulation of the tubular amiloride-sensitive Na^+/H^+-exchanger may,[10] in part, contribute to the increased sodium resorption, in addition to alterations of intrarenal perfusion patterns.[11] Angiotensin II, acutely, also causes the mesangial cells to contract, thereby contributing to the acute reduction in the ultrafiltration coefficient of the glomerular capillary surface area.[12] This acute effect on the mesangium combines with the proliferative action of angiotensin II on cell growth and interstitial tissue expansion when the stimulation of the renin angiotensin system is maintained for longer periods, such as in heart failure.

The less beneficial, or even potentially detrimental effects of angiotensin II on the kidney result from the same basic mechanism, i.e., the increase of intraglomerular pressure and the proliferation of mesangial cells. Progressive glomerular sclerosis has been ascribed to prolonged preferential vasoconstriction of the efferent arteriole.[13,14]

Hence, high angiotensin II levels in heart failure are certainly not protective for the systemic circulation, where they are known to trigger a vicious cycle, although they act in a compensatory fashion on the kidney. However, the goal of maintaining renal excretory function is achieved only at the expense of detrimental effects during the long term. These include progressive glomerular sclerosis with a substantial anatomic, not just functional, loss of excretory capacity.

Effect of ACE inhibitors on kidney function in heart failure: The reversal of angiotensin II-mediated effects on kidney function in heart failure would be expected to consist of a decrease in filtration fraction. In fact, a decrease in filtration fraction of about 12% was a consistent finding of ACE inhibitor therapy in our patients with heart failure. This was the consequence of a small reduction in glomerular filtration rate (−7% or −4%, respectively) accompanied by an increase in renal plasma flow of about 6%. These results are consistent with the preferential withdrawal of the vasoconstrictor tone at the efferent arteriole by ACE inhibition, thereby reducing intraglomerular capillary pressure and hence filtration fraction. ACE inhibition in heart failure may influence renal function, not only by changing the tone of the efferent arteriole but, in addition, by increasing cardiac output and simultaneously decreasing renal perfusion pressure (Figure 3).

Episodes of symptomatic hypotension were not observed in patients treated with lisinopril or captopril in this study. However, mean arterial pressure decreased by >50 mm Hg in individual patients, reaching values as low as 60 mm Hg. It has been speculated that the degree of ACE inhibitor-induced blood pressure reduction is the cause for poor end-organ perfusion, e.g., impairment of renal function. Reduction of cerebral and renal perfusion pressures below the threshold of autoregulation clearly would lead to a progressive decrease in renal flow. Therefore, this study investigated whether the degree of blood pressure reduction

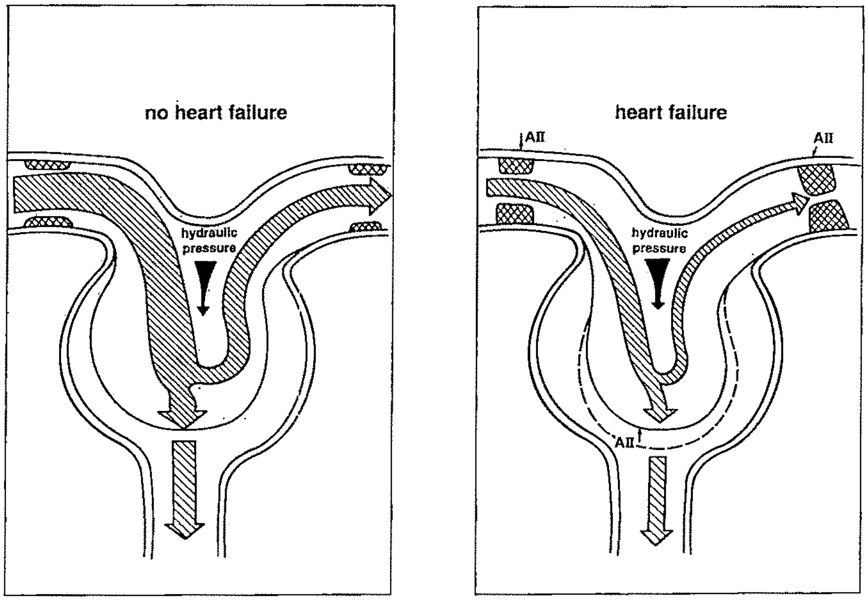

FIGURE 2. Changes in renal hemodynamics in heart failure compared with a state with normal pump function. AII = angiotensin II.

following ACE inhibitor administration caused a critical reduction of glomerular filtration rate or renal plasma flow. Since no relations between these variables were found, it may be concluded that blood pressure reduction itself in these patients could not have accounted for the changes observed in renal function. It should be noted, however, that at the end of the titration period glomerular filtration rate was positively related to mean arterial pressure.

Although the slope of this regression line was flat, it may be indicative of the action of ACE inhibitors, both on blood pressure and glomerular filtration rate. This assumption is supported by the lack of any relation between these parameters prior to the administration of ACE inhibitors. It is further reinforced by the observation of a significant inverse relation between mean arterial blood pressure and renal plasma flow at the end of the titration period, a correlation that was not observed for either parameter on day 0. The development of relations between blood pressure and glomerular filtration rate or renal plasma flow during ACE inhibitor treatment may be taken as evidence for their mode of action: the higher the degree of unloading of the heart, the higher also the degree of unloading of the kidney, with the consequence of increasing renal plasma flow but decreasing glomerular filtration rate.

Long-acting versus short-acting ACE inhibitors in heart failure: Extensive and prolonged lowering of blood pressure in heart failure is a possible mechanism for the induction of functional renal impairment. Hence, by their pharmacokinetic profile long-acting ACE inhibitors are prone to produce impairment of renal function more often. This has been described with high fixed doses of ACE inhibitors that were administered to patients with severe heart failure, but where no adjustment of the dose of diuretics was allowed.[7] The lower and clinically more relevant dosage used in this study for captopril and lisinopril combined with a careful stepwise titration even in moderate heart failure did not produce increases in serum creatinine, which might give rise to discontinuation of ACE inhibitor therapy. During the observation period of 5 days, serum creatinine remained stable at 1.1 or 1.2 mg/dL. Only 1 patient from each group developed increases of serum creatinine ≥0.4 mg/dL.

In a large multicenter study[15] the long-acting ACE inhibitor enalapril has been administered to patients with severe heart failure (NYHA class IV). In a retrospective analysis, it became clear that the patients receiving placebo with more severe impairment of renal function at the beginning had an even worse prognosis. This was in contrast to the group receiving the long-acting ACE inhibitor. A similar reduction in renal function was not a predictor of poor outcome in this group, and there was even a tendency for improved survival when patients received enalapril.[16] This dissociation of the prognostic impact of impaired renal function in severe heart failure may lead to the following conclusions: (1) it is safe to administer ACE inhibitors to patients with heart failure and an impaired renal function, and (2) not giving ACE inhibitors to these patients would worsen their prognosis.

The changes in renal function induced by ACE

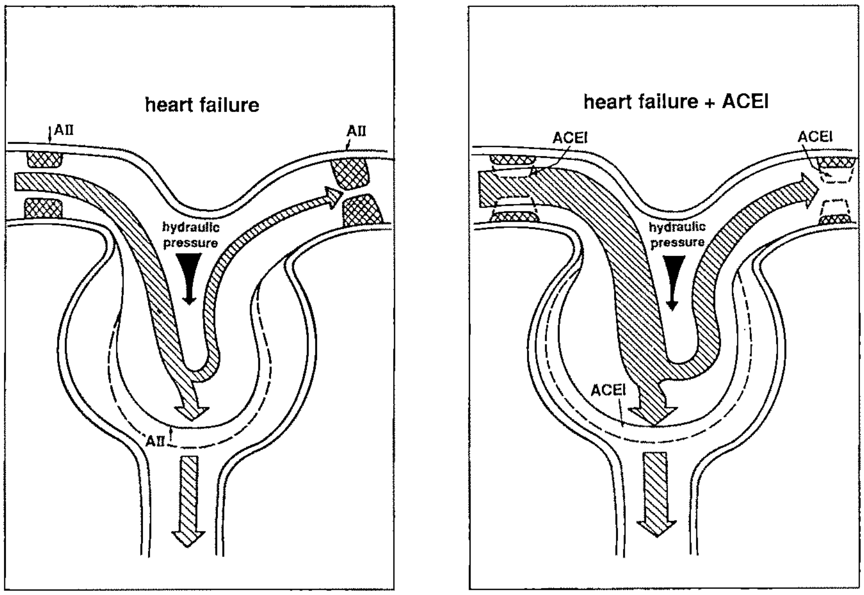

FIGURE 3. Changes in renal hemodynamics induced by angiotensin-converting enzyme inhibition (ACEI) in patients with heart failure. AII = angiotensin II.

inhibitors are clinically judged from alterations in serum creatinine. Swedberg[16] regarded increases in serum creatinine after initiation of therapy with ACE inhibitors as evidence for adequate ACE inhibition. In patients with severe heart failure, serum creatinine increased by about 10% within 2 weeks of initiating enalapril therapy. The increase seemed to be independent of the baseline creatinine concentrations.[16] Based on the data from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), it was suggested that the dose of the ACE inhibitor need not be changed when increases of serum creatinine of $<30\%$ of baseline values are observed.[16] When long-acting ACE inhibitors are given to patients with severe heart failure in high doses without adjusting the dose of diuretics the increase in serum creatinine may be more pronounced.[7] Administration of ACE inhibitors to patients with severe heart failure, however, is not associated with a higher risk, but even with an improvement of survival.

Effect of inhibitors of prostaglandin synthesis on kidney function in patients with heart failure receiving ACE inhibitors: In a retrospective analysis, renal function data obtained from 31 patients during the initiation period of ACE inhibition were reviewed. The addition of acetylsalicylic acid to the therapeutic regimen appears to be associated with a higher risk of renal impairment: the decrease in glomerular filtration rate was more marked and the compensatory increase of renal plasma flow otherwise observed was no longer detectable. This observation requires confirmation from prospective studies. However, it may be speculated that inhibition of prostaglandin synthesis in patients with heart failure may critically interfere with kidney function, especially when ACE inhibitors are given concomitantly (Figure 4). Most likely, the reduction of renal resistance induced by ACE inhibition, through vasodilation of both efferent and afferent arterioles, is attenuated because of lack of prostaglandin mediated afferent vasodilation. Inhibition of prostaglandin synthesis showed a similar pattern on the peripheral circulation in these patients, i.e., the beneficial effects of ACE inhibitors—reduction of afterload and increase in cardiac output—were attenuated and the clinical condition deteriorated.[17]

Thus, the coadministration of prostaglandin synthesis inhibitors should be considered very carefully in patients with severe heart failure receiving ACE inhibitors and diuretics.

Practical considerations for the use of ACE inhibitors in heart failure: Several lessons have been learned from past experience regarding the use of ACE inhibitors in heart failure.

DOSAGE: The risk of inducing functional renal impairment and symptomatic hypotension is dose dependent and small doses should be given, especially at the beginning of ACE inhibitor therapy. In the CONSENSUS trial, unwanted effects of enalapril were markedly reduced when only half of the initial dose (2.5 instead of 5 mg) was given.[15] In our study, therefore, we performed a dose titration during the initiation of therapy.

PHARMACOKINETICS: An ACE inhibitor with a short elimination half-life will allow the systemic renin angiotensin system to recover intermittently, thereby leading to blood pressure increases. Hence, the goal of a continuous unloading of the heart is more difficult to achieve with a drug of short half-life compared with one with a longer half-life.

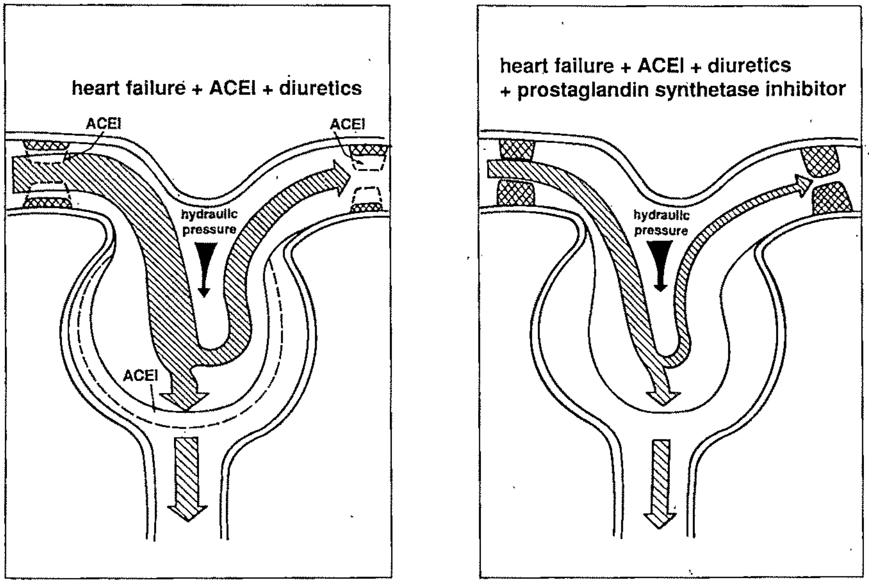
heart failure + ACEI + diuretics
ACEI
ACEI
hydraulic pressure
ACEI
heart failure + ACEI + diuretics
+ prostaglandin synthetase inhibitor
hydraulic pressure

FIGURE 4. Changes in renal hemodynamics induced by inhibitors of prostaglandin synthesis on top of angiotensin-converting enzyme inhibition (ACEI) plus diuretics in patients with heart failure.

If renal perfusion becomes pressure dependent (and ACE inhibition has lowered blood pressure below the autoregulation threshold), then intermittent increases in blood pressure seem to be desirable. However, the data presented in this study make it rather unlikely that long-acting ACE inhibitors would reduce blood pressure levels in patients with moderate heart failure (NYHA II–III) to a degree that renal function is directly compromised.

DIURETICS: Serum creatinine may increase after the initiation of ACE inhibitor therapy in heart failure. When this increase is considered to be of clinical significance, it seems wise to reduce the concomitant dose of diuretics first.[7] The higher the dose of diuretics, the more marked becomes the stimulation of the renal renin–angiotensin system, and, hence, the dependence of filtration on angiotensin II–induced efferent vasoconstriction. Reduction of diuretic dosage may attenuate this stimulation of vasoconstrictor forces while, simultaneously, the beneficial effects of ACE inhibitors on cardiac function can be maintained.

Those patients who belong to the high-risk group for developing functional renal insufficiency (patients with hyponatremia, high doses of diuretics, low cardiac output, diabetes mellitus) are generally those who would also benefit from ACE inhibition.[18] They will usually respond to this kind of therapy with an increase in serum creatinine. This should be interpreted as an indicator of the action of the drug, working also in the kidney. The meaning of serum creatinine increase is different from that observed in patients with heart failure not receiving an ACE inhibitor, where, in general, it indicates a progression of heart failure and activation of vasopressor systems. In patients with hypertension and impaired renal function on conventional antihypertensive therapy, an increase in serum creatinine indicates the progressive loss of renal excretory capacity. In contrast, comparable patients on ACE inhibitors do show an initial transient increase in serum creatinine, but the latter course is characterized by retardation of progressive renal impairment.[19]

Hence, an increase in serum creatinine (within a certain range) should not be taken as an equivalent of renal failure in patients on ACE inhibitors with impaired pump function. It indicates that the drug is working, not the loss of physiologically active renal tissue. With these considerations in mind, it is possible, in most cases classified as high risk, to titrate the doses of ACE inhibitors and diuretics to produce substantial benefit for severely ill patients.

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Heart Failure in 2001: A Prophecy

Arnold M. Katz, MD

Understanding of heart failure has developed through 3 paradigms involving organ, cell, and gene. The first views heart failure as an abnormality of *organ* (pump) function leading to salt and water retention and vasoconstriction. Therapy to correct these circulatory abnormalities is well accepted and effective. The second considers heart failure as a disordered *cellular* function, mainly impaired contraction and relaxation. Efforts to correct the biochemical and biophysical abnormalities responsible for these disorders of myocardial performance have, however, been less successful. Recent emphasis on efforts to improve prognosis as well as symptoms in patients with chronic heart failure demonstrates that it is a lethal disease with problems of survival similar to those in malignancies. The third paradigm of abnormal *gene* expression, which in the failing heart represents a cardiomyopathy of overload, appears to be a major cause of poor prognosis in these patients. Evidence that the angiotensin-converting enzyme inhibitors have important effects on cell growth, as well as on vascular tone, suggests that their ability to prolong survival in patients with heart failure may be due largely to the inhibition of detrimental effects of angiotensin II on cardiac gene expression. Thus, it seems likely that work focused on the third paradigm will uncover specific abnormalities of gene expression that are responsible for poor survival of patients with heart failure. By 2001, I predict that heart failure will be viewed as an abnormality of cell growth and this will lead to the development of therapies to retard, if not reverse, the clinical deterioration. Using the tools of molecular biology, cardiologists will not only prolong survival in heart failure but, at the same time, will be able to improve symptoms and so increase the well-being of these patients.

(Am J Cardiol 1992;70:126C–131C)

Because the clinical picture in heart failure is dominated by signs and symptoms caused by abnormal circulatory hemodynamics, today's physician treats this increasingly common condition with the primary goal of minimizing abnormalities that are, in reality, secondary to impaired pump function. However, it is now clear that the dyspnea, fatigue, and anasarca that most commonly bring these patients to the physician are, in fact, consequences and not causes of the underlying condition. Thus, treatment to increase cardiac output and to decrease systemic and pulmonary venous pressures addresses quite different abnormalities from those that underlie the pathophysiology in most patients with heart failure.

The central prophecy of this article is that by the year 2001 physicians will be better able to treat the real problem in heart failure, which lies not in the disordered circulation, but instead is progressive deterioration of the failing myocardium.[1] For this reason, I predict that therapy of heart failure, while continuing to alleviate symptoms, will focus on the myocardial abnormalities that shorten the survival of the cells of the failing heart and so are responsible for both the progressive downhill course and premature death in patients with heart failure.

THREE PARADIGMS CHARACTERIZE THE CHANGING CLINICAL APPRECIATION OF HEART FAILURE

Prophecy requires an appreciation of both where we are and where we have been; only then can we draw a trajectory into the future. During this century, our understanding of heart failure has evolved through 3 paradigms that can be defined briefly as: organ, cell, and gene (Table I).[2] The first paradigm, which dominated thinking in the first half of this century, viewed heart failure as an abnormality of the cardiac pump in which reduced ejection and impaired filling led to such circulatory responses as salt and water retention. The demonstration in the early 1960s that myocardial contractility is depressed in the failing heart turned our attention to the second paradigm, which considers heart failure as a disorder of cellular function. Rapid advances in our understanding of the inter-

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actions between the contractile proteins and their control by excitation–contraction coupling led cardiologists to view heart failure in terms of the calcium fluxes responsible for contraction and relaxation. This paradigmatic shift redirected goals of therapy to biochemical abnormalities responsible for the depressed pumping action of the failing heart. However, it is now apparent that inotropic therapy can worsen prognosis in patients with chronic heart failure.[3] This unfortunate finding reflects the fact that the fundamental problem in heart failure is neither a reduction in the pumping action of the failing heart nor a defect in the calcium fluxes that activate and inactivate the interactions between the heart's contractile proteins. Instead, the major problem is the progressive downhill course in these patients, which now appears to be due to alterations in the myocardium itself.

Appreciation that heart failure is a lethal disease, in which survival is similar to that in many malignancies, has led to yet another paradigmatic shift in which therapy is coming to focus on abnormalities in the failing myocardium. Accelerated myocardial cell death, which follows chronic overload of any cause, is probably due in part to energy starvation in the cells of the failing heart. However, alterations involving the third paradigm—abnormal gene expression, as well as abnormal cellular energetics—now appear to play an important role in the pathophysiology of heart failure. Thus, there is growing evidence that ventricular hypertrophy, while initially adaptive by increasing the mass of the failing heart, becomes maladaptive as the result of chronic alterations of protein synthesis and membrane assembly. The latter changes, which are associated with reduced cell survival in the failing heart, represent a cardiomyopathy of overload that appears to be a major cause of the poor prognosis in these patients.[1] Any prophecy as to future directions in the therapy of heart failure must therefore be based on predictions as to future evolution of our appreciation of the pathophysiology of this clinical syndrome.

TABLE I Three Paradigms in the Evolution of Cardiovascular Regulation

Paradigm	Regulation of Cardiac Performance	Angiotensin Actions	Heart Failure
Organ physiology	Changing end-diastolic fiber length (Starling's law of the heart)	Blood pressure regulation	Salt and water retention, vasoconstriction
Cell biochemistry	Changing myocardial contractility, calcium fluxes	Increased smooth and cardiac muscle tension, calcium fluxes	Impaired myocardial contractility and relaxation
Gene expression	Altered synthesis of myocardial proteins	Increased vascular and myocardial growth, hypertrophy	Myocardial alterations, "cardiomyopathy of overload"

THE FIRST PARADIGM: TREATMENT OF HEART FAILURE AS AN ABNORMALITY OF ORGAN FUNCTION

Salt and water retention: Until the late 1950s, when lack of effective diuretics made fluid retention the major clinical problem in patients with heart failure, the focus of therapy was on the kidney. The accidental discovery in 1920 that a mercurial used to treat syphilitic heart disease caused diuresis[4] initiated >30 years of emphasis on the renal abnormalities responsible for salt and water retention in these patients. Success in these efforts has given us an array of powerful diuretics that can remove excess salt and water from virtually every patient with heart failure. Unfortunately, however, effective diuresis in patients with severe heart failure can produce a low output state that is accompanied by renal and hepatic failure. This, of course, reflects the fact that removal of salt and water from patients with heart failure does not alter the underlying disease.

PROPHECY FOR 2001: The efficacy of currently available diuretics is such that I do not predict major advances in this aspect of the therapy of heart failure. The value of any approach to diuresis is limited by the fact that reducing the volume of the venous reservoirs inevitably depletes arterial volume and so also reduces cardiac output. This, of course, limits the efficacy of diuretic therapy today, and it seems unlikely that any new diuretic can overcome this inherent limitation.

Vasoconstriction: A second approach to the therapy of heart failure, which centers on the heart rather than the kidney, was based on early observations that arterial vasodilators had a beneficial effect in patients with heart failure.[5–7] Understanding of the maladaptive nature of chronic vasoconstriction had led to the widespread use of vasodilators in the management of both acute and chronic heart failure. The value of these drugs lies not only in the ability of unloading the failing heart to increase cardiac output,[8] but also the fact that vasodilation reduces myocardial energy requirements. As discussed later, in terms of modifying survival in patients with heart failure not all vasodilators are created equal.

PROPHECY FOR 2001: There remains much mystery regarding the different vasodilators, largely because of remarkable differences in their effects on prognosis in patients with heart failure. I predict that the obvious energy-sparing effects of afterload reduction will not turn out to be the major reason that some members of this class of drugs prolong survival in this condition (see below). However, we can expect to see the development of new selective vasodilators to improve perfusion in selected arterial beds.

THE SECOND PARADIGM: TREATMENT OF HEART FAILURE AS AN ABNORMALITY OF CELLULAR FUNCTION

Although treatment of the circulatory responses to heart failure remains the cornerstone of therapy for this condition, at least in terms of symptom relief, abnormalities in the biochemistry and biophysics of heart muscle play an important role in virtually every patient with heart failure. Even when pump performance is impaired by such anatomic disorders as a damaged valve or a large dyskinetic area following myocardial infarction, chronic overloading of active myocardial cells leads to important biochemical abnormalities that play an important role in the pathophysiology and prognosis of heart failure.[1]

Energy starvation in the failing heart: Among the most important of the biochemical changes in the overloaded cells of the failing heart is an imbalance between energy production and energy utilization. The most obvious cause for this imbalance is, of course, the overload itself, which increases myocardial energy expenditure. At the same time, changes in the hypertrophied heart limit chemical energy production. Together, excessive energy demand and impaired energy production in the failing heart engender a state of "energy starvation," especially when cardiac work is increased. This imbalance is exacerbated by structural changes in the hypertrophied heart that decrease capillary density, reduce the number of mitochondria, and increase the amount of connective tissue.[1] Together, these abnormalities explain decreased myocardial high energy phosphate contents seen in both animal models of heart failure and in biopsies of hypertrophied human hearts.[9–13]

Energy starvation causes both systolic and diastolic dysfunction in the failing heart, due largely to attenuation of allosteric (regulatory) effects of adenosine triphosphate (ATP) that accelerate the calcium fluxes involved in both contraction and relaxation.[14] The result is impaired systolic (inotropic) and diastolic (lusitropic) function that contributes to the impaired pump performance described by the first paradigm.

PROPHECY FOR 2001: Efforts to correct any energy imbalance are, of course, constrained by the laws of thermodynamics, so that we must either reduce energy demands or increase energy production. As already noted, vasodilator therapy represents a rational approach to lowering energy demands. However, certain classes of vasodilators, for example the α-adrenergic agonists, do not improve prognosis in patients with heart failure.[15] This supports my view that new vasodilators designed simply to improve energetics have little promise. Means to increase myocardial energy production in the failing heart are not obvious, and I doubt if any new substrate or metabolic regulator will prove useful in these patients. Energy production might be facilitated by selective coronary vasodilation; however, this seems to be a "long shot" because coronary flow in the failing heart is limited mainly by microvascular abnormalities and the high intramyocardial tension caused by the abnormal geometry of the hypertrophied ventricle. A quite different approach to improving the energy balance in the failing heart, reducing energy expenditure, is discussed below.

Depressed contractility: The finding that contractility is reduced in the failing heart[16] led to the logical conclusion that inotropic stimulation would benefit patients with heart failure. However, as I had suggested almost 20 years ago,[17] this prediction overlooks important aspects of the pathophysiology of heart failure. Although useful in the short-term management of acute heart failure, inotropic drugs that increase cellular levels of cyclic adenosine monophosphate (cyclic AMP) shorten survival in patients with chronic congestive heart failure.[3] These harmful effects may be due in part to cell damage caused by increased energy expenditure. In addition, inotropic drugs that act by increasing cytosolic calcium and cyclic AMP concentrations in the myocardium are likely to be arrhythmogenic.[18]

PROPHECY FOR 2001: I see no future in inotropic therapy for chronic heart failure, and available evidence has sounded what appears to be the death knell for drugs that increase myocardial cyclic AMP levels. I also foresee little clinical value for other approaches to inotropic stimulation of the chronically failing heart. Drugs that increase cytosolic calcium—for example, by increasing the calcium sensitivity of the contractile proteins or blocking potassium channels so as to prolong the action potential—would seem to carry the inevitable side effect of worsening important relaxation abnormalities commonly seen in patients with heart failure (see below). I hasten to exclude digitalis from this blanket condemnation because I do not view this drug as primarily a direct inotrope; instead, there is compelling evidence that the cardiac glycosides have important centrally mediated vasodilator and negative chronotropic actions that would be energy sparing to the failing heart.[19,20] In this context, I give short odds that the current multicenter trial on the effects of digitalis on survival will show this drug to reduce mortality, a prediction that reflects my view that increased parasympathetic tone is beneficial to the overloaded, failing myocardium.

Negative inotropic agents: Although the role of negative inotropic agents, and especially the β-adrenergic blockers, in the management of heart failure remains controversial, several reports indicate that these drugs can improve symptoms and cardiac function.[21–25] Further, there is general agreement that negative inotropic agents prolong survival in one subset of patients. This is, of course, patients with left ventricular dysfunction following myocardial infarction, where β blockade clearly improves prognosis. Furthermore, negative inotropic drugs have gained wide acceptance in the treatment of patients with hypertrophic cardiomyopathies, both primary (idiopathic) and secondary to chronic hypertension.

PROPHECY FOR 2001: I predict that β blockers will be found to be valuable in improving prognosis in patients with heart failure, especially when given early, before the myocardium has deteriorated severely. The rationale for my prediction is 2-fold. The first is the obvious benefit of slowing energy expenditure in myocardial cells that are in an energy-starved state, as appears to be the case for the failing heart (see above). Second, cyclic AMP, the intracellular messenger generated by the sympathetic nervous system, may participate as a stimulus for maladaptive cell growth; as a result, therapy that attenuates this signal should be beneficial in patients with heart failure. Thus, by 2001, β-adrenergic blockers could become first line therapy in both mild heart failure and in patients with more advanced left ventricular dysfunction who are able to tolerate these drugs.

Overall, I see cardiology as on the threshold of a major shift in thinking similar to that in the 1950s and 1960s, when vasodilators instead of vasoconstrictors came to be used in the management of cardiogenic shock,[26] and a few years ago when suppression of nonlethal arrhythmias was found to increase, rather than decrease, the risk of sudden death following myocardial infarction.[27] Thus, my prophecy is that by 2001 our approach to therapy of heart failure will have turned 180 degrees, from positive to negative inotropic agents.

Impaired relaxation: It is now clear that lusitropic abnormalities play an important role in the pathophysiology of heart failure, but there is virtually no experience with drugs designed to improve relaxation. This is due in part to serious theoretical problems in developing a drug that would accelerate relaxation. Most important is the fact that relaxation, which is mediated largely by active calcium transport out of the cytosol by the sarcoplasmic reticulum,[14] is energy dependent. To accelerate this calcium pump raises theoretical problems in the energy-starved failing heart that are similar to those discussed earlier in regard to positive inotropes. On the other hand, drugs that facilitate relaxation by decreasing the calcium sensitivity of the contractile proteins have theoretical advantages, even though they would reduce contractility.

PROPHECY FOR 2001: The theoretical considerations just discussed lead me to predict that in 2001 we will be using agents to promote relaxation in the failing heart by reducing the calcium sensitivity of the cardiac contractile proteins. We may also have improved means to slow, or reverse, connective tissue abnormalities that reduce ventricular compliance (see below). However, I hold little hope for drugs that directly stimulate the calcium pump of the cardiac sarcoplasmic reticulum because they could worsen the state of energy starvation in the failing heart.

THE THIRD PARADIGM: TREATMENT OF HEART FAILURE AS AN ABNORMALITY OF CARDIAC GENE EXPRESSION

It is now apparent that changes in the composition of the hypertrophied heart play an important role in determining the poor long-term survival of patients with heart failure. There is growing evidence that once overlooked abnormalities in the hearts of these patients play a key role in determining prognosis, which is influenced by deterioration of the myocardium that culminates in myocardial cell death.[1] Two interrelated aspects of the myocardial response to overload probably explain this poor prognosis. As already noted, chronically increased energy demands and impaired energy production together lead to a state of energy starvation that probably contributes to the pathogenesis of both the lethal arrhythmias and cardiac deterio-

TABLE II Effects of Various Classes of Vasodilator on Prognosis in Patients with Chronic Heart Failure[33,34]

Vasodilator	Effect of Prognosis
Converting enzyme inhibitors	Marked improvement[35–39]
Nitrates plus hydralazine	Some improvement[15]
α-Adrenergic blockers	No improvement[15]
Calcium channel blockers	Probably detrimental[33,40]
"Inodilators"	Detrimental[3]

TABLE III Possible Mediators of the Signal that Initiates Hypertrophy in the Overloaded Heart

Cell deformation	Stretch-activated ion channels
	Cytoskeletal rearrangements (microtubules, desmin)
Extracellular growth factors	Fibroblast growth factor
	Transforming growth factor β
Extracellular neurotransmitters and hormones	α-Adrenergic agonists
	β-Adrenergic agonists
	Angiotensin II
	Thyroxine
	Insulin
	Growth hormone
	Glucocorticoids
Intracellular energy deficit	Decreased high energy phosphates, ATP, phosphocreatine
	Increased products of excessive energy utilization ADP, AMP, creatine
Intracellular second messengers	Cyclic AMP, cyclic AMP-dependent protein kinases
	Calcium
	Inositol tris phosphate
	Diacylglycerol, protein kinase C
Cellular proto-oncogenes	*c-fos*, *c-myc*, *c-jun*

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.
Adapted from Katz.[14]

ration in these patients. A second aspect of the myocardial response to overload, which is related to abnormal growth patterns in the overloaded heart, also appears to shorten the life span of hypertrophied myocardial cells. This results from complex, and still incompletely understood, changes in gene expression that alter the synthesis of a number of key myocardial proteins.[28–31]

Among the most significant of the changes in the composition of the failing heart is the preferential synthesis of fetal isoforms of several proteins. This probably reflects the fact that the cells of the adult myocardium, which are unable to divide, normally synthesize protein at only a very slow rate. Thus, when the adult heart is stimulated to grow by a hemodynamic overload, it appears to pay a "price": in order to accelerate protein synthesis to rates normally seen only during fetal and early neonatal life, many newly synthesized proteins revert to isoform patterns seen earlier in development. It is possible that preferential synthesis of fetal protein isoforms in the overloaded heart leads to the appearance of myocardial cells that "wear out" at an accelerated rate, thereby contributing to the deterioration of the myocardium in patients with heart failure. Abnormalities in the connective tissue of the cardiac skeleton may also be important in determining prognosis in the patient with heart failure.[32]

One aspect of the altered myocardial composition in the patient with heart failure is suggested by the surprising finding that not all vasodilators improve prognosis in patients with heart failure (Table II).[15,33–40] These differences indicate that actions other than afterload reduction and a concomitant decrease in energy expenditure account for divergent effects of various vasodilator drugs on survival.

A clue as to the mechanism of a beneficial "side effect" of certain vasodilators, which I believe to be the real mechanism for the salutary effects of the angiotensin-converting enzyme (ACE) inhibitors in patients with heart failure,[41] is found by examining a list of putative mediators of the growth response to overload (Table III). Many of these mediators are, in fact, the extracellular and intracellular messengers that mediate the neurohumoral influences that stimulate the failing heart. For example, β-adrenergic agonists and the second messenger cyclic AMP are not only chronotropes and inotropes, but also promote cardiac growth. Similarly, angiotensin II, a weak inotrope whose production is blocked by ACE inhibitors, is a growth promoter whose effects are mediated by 2 intracellular messengers: diacylglycerol and the inositol phosphates.[14] As already noted, inhibition of angiotensin formation is of remarkable benefit in heart failure. Vagal stimulation and nitrates, whose effects are mediated by the inhibitory guanosine coupling protein (G_i), may exert salutary effects that inhibit maladaptive growth. This is not, however, a simple story; for example, α-adrenergic agonists, which generate the same intracellular messengers as angiotensin II, do not appear to improve survival in heart failure.[15] Clearly, there is much to learn in this important area.

PROPHECY FOR 2001: This is on the one hand the easiest of my predictions, for I have no doubt that effects other than vasodilation account for the remarkable ability of the ACE inhibitors to prolong life in patients with heart failure. It is safe to say, therefore, that by 2001, improved understanding of these effects will be translated into improved therapy for heart failure. Much more difficult, indeed impossible, is to predict exactly how this will be done. Almost certainly, we will see the introduction of angiotensin II blockers, which should avoid some of the side effects of the current ACE inhibitors. As suggested earlier, interventions such as β blockade and vagal stimulation, as well as therapy with ACE inhibitors, may exert beneficial effects on the failing heart by inhibiting maladaptive growth. Yet, as is apparent from the list of growth mediators in Table III, the complexity of this third paradigm is, to the say the least, dazzling.

My final prophecy, therefore, is a general one: that investigators over the next decade will dissect and understand the regulation of both adaptive and maladaptive myocardial growth and that this harvest of new knowledge will lead to new therapeutic approaches that will be of benefit to the patient with heart failure.

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First-Dose Blood Pressure Response in Mild-to-Moderate Heart Failure: A Randomized, Double-Blind Study Comparing Enalapril with Lisinopril by 24-Hour Noninvasive Blood Pressure Monitoring

Jan Erik Otterstad, MD, PhD, and Gisle Froeland, MD

Angiotensin-converting enzyme (ACE) inhibitors are valuable in the treatment of heart failure.[1] They are frequently used after diuretic and/or digitalis treatment has failed to alleviate all the symptoms of the syndrome.[2] However, a well-known problem in their use is hypotension observed on the first dose of the ACE inhibitor, especially in patients who are salt and water depleted by prior use of loop diuretics.[3,4] This has been a problem in initiating ACE inhibitor therapy in major trials.[5] It is possible that one reason for first-dose hypotension is the relatively rapid onset of action of the most widely used ACE inhibitors, captopril and enalapril. Lisinopril is absorbed slowly and has a gradual onset of action.[6] This slower onset of action could theoretically lead to a reduced risk of first-dose hypotension by producing more gradual decreases in blood pressure, which could be adequately compensated for by the body.

In this present study we have evaluated the initial blood pressure response to the first dose of lisinopril or enalapril in patients with mild-to-moderate heart failure using ambulatory blood pressure monitoring.

This investigation was part of a multicenter study comparing the effect of lisinopril and enalapril on exercise duration in heart failure, the results of which are reported by Zannad et al elsewhere in this Symposium.

METHODS

Of 20 patients originally recruited in our study center, 15 consented to undergo ambulatory blood pressure monitoring at the start of randomized double-blind treatment with either lisinopril or enalapril. The inclusion and exclusion criteria employed in their selection are detailed elsewhere in this Symposium by Zannad et al. Baseline data were obtained during a 14-day prerandomization run-in period during which placebo was given. In addition to ambulatory blood pressure recording, conventional blood pressure and heart rate measurements were made while sitting and after 5 minutes in the standing position. Ambulatory blood pressure measurements were made as described previously.[7] A series of 6 measurements per hour were made while the patients were awake and 2 per hour while they were asleep.

Coincident with the start of ambulatory monitoring, patients took lisinopril 2.5 mg or enalapril 2.5 mg and a further 5 mg dose of the appropriate drug a mean of 16 hours after the first dose. In all but 1 patient, ambulatory monitoring was started in the afternoon.

Data from the 24-hour monitoring were analyzed by dividing the monitoring period into 3 time bands: (1) from the start of monitoring to the time of sleep (mean 7 hours); (2) from the start of sleep to the intake of the second dose (mean 9 hours); and (3) from the intake of the second dose to the end of the monitoring period (mean 8 hours).

Patients were asked to report any newly occurring symptoms experienced and emphasis was placed on the possibility of vertigo or syncope.

The diurnal blood pressure curves for systolic and diastolic blood pressures were constructed from arithmetic means of the hourly means of the individual patients. The effect of treatment on blood pressure was estimated against baseline values for systolic and diastolic blood pressure. One baseline measurement was taken in the seated position using the monitoring equipment before

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the first dose was taken, and a second measurement was made 1-hour postdose while the patients were ambulatory. An unpaired 2-tailed *t* test was used to assess the statistical differences in treatment effects. For the second time band (during which the patients were asleep), the average systolic and diastolic blood pressures were compared between the 2 treatments using the same *t* test. For the third time band, blood pressure readings taken for the first hour after the second dose of medication were used as a baseline value.

RESULTS

The demographic characteristics of the patients are shown in Table I. There were no significant differences between the 2 groups apart from a higher serum creatinine concentration in the patients randomized to enalapril. The serum creatinine levels for both groups of patients were in the normal range.

Diurnal blood pressure curves for both lisinopril- and enalapril-treated patients are shown in Figure 1. The average systolic and diastolic blood pressures over the whole 24-hour period for lisinopril and enalapril were 123 ± 29/64 ± 9 and 116 ± 14/66 ± 7 mm Hg, respectively. There were no significant between-treatment differences. When blood pressures after the first dose were compared with the blood pressures monitored during the first hour after ingestion, both systolic and diastolic pressures were more reduced by enalapril than lisinopril compared with baseline values and this became significant for diastolic pressure 7 hours postdose ($p = 0.03$; Figure 2). For the entire period of 2–7 hours postdose, the difference between the effects of the 2 drugs on diastolic pressure was marginally significant ($p = 0.07$; Figure 2). Systolic pressures were not significantly different from baseline for either drug.

When sitting pretreatment blood pressure was used as the baseline reference point, no intertreatment differences in the effects on diastolic or systolic pressures were observed, although the trend toward lower blood pressures with enalapril was still apparent.

During the period of sleep, the mean blood pressures for lisinopril and enalapril were 114 ± 33/59 ± 10 and 104 ± 12/61 ± 5 mm Hg. No significant differences were observed ($p = 0.24$ and $p = 0.88$, respectively).

The additional dose of enalapril and lisinopril at the start of the third time band produced only negligible changes in blood pressure with no intertreatment differences.

TABLE I Baseline Data in the 14 Patients, 7 Randomized to Enalapril and 7 to Lisinopril, Who Completed 24-Hour Blood Pressure Monitoring Following First Dose of Active Therapy

Paramter	Enalapril (n = 7)	Lisinopril (n = 7)
Age [yr, mean (range)]	68 (61–76)	69 (55–81)
Weight [kg, mean (range)]	81 (68–97.5)	78 (68.5–92)
Standing SBP [mm Hg, mean (range)]	133 (125–145)	132 (115–160)
Standing DBP [mm Hg, mean (range)]	78 (70–90)	82 (70–95)
NYHA class [mean (range)]	2.4 (2–3)	2.6 (2–3)
Atrial fibrillation	1	3
Postinfarction failure	7	5
Cardiomyopathy	0	1
Valvular heart disease	0	1
Furosemide treatment	6	7
Furosemide dose [mg, mean (range)]	50 (40–80)	43 (10–80)
Digitalis treatment	7	5
Long-acting nitrates	4	4
Warfarin	3	2
Aspirin	1	3
Other drugs	1 (amiodarone)	0
Minutes of exercise [mean (range)]	9 (7–10)	9 (6–12)
Hemoglobin [g/dL, mean (range)]	14.9 (12.5–16.9)	14.7 (12.9–16.4)
Serum creatinine [mmol/liter, mean (range)]	124 (107–155)	101* (68–131)
Serum potassium [mmol/liter, mean (range)]	4.7 (4.1–5.1)	4.3 (4.0–4.6)
Serum sodium [mmol/liter, mean (range)]	142 (138–145)	142 (140–146)

*p = 0.03.
DBP = diastolic blood pressure; NYHA = New York Heart Association; SBP = systolic blood pressure.

No clinically detectable hypotensive symptoms were noted with the exception of 1 patient randomized to lisinopril who reported vertigo for 3–5 hours after taking the second (5 mg) dose of the drug. During that period his systolic blood pressure ranged from 75–80 mm Hg but remained >90 mm Hg for the remaining hours of monitoring.

DISCUSSION

The difference noted between the effects of lisinopril and enalapril on first-dose blood pressure may reflect the difference between the speed of absorption of the 2 drugs. Enalapril is relatively rapidly absorbed and undergoes hydrolysis to produce enalaprilat. Peak blood levels of enalaprilat, the active ACE inhibitor, usually occur 4 hours

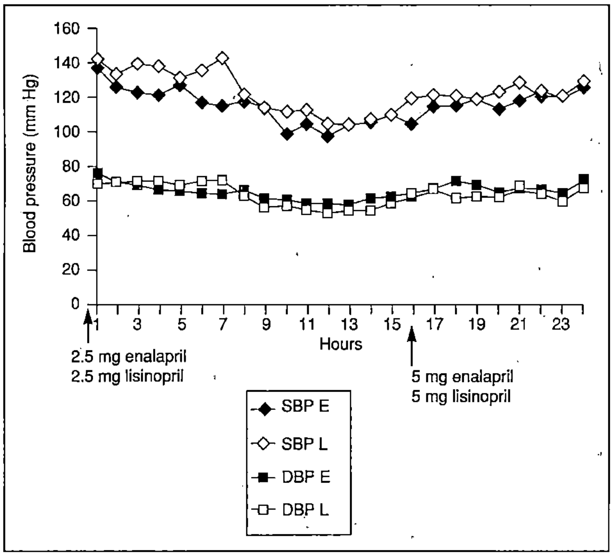

FIGURE 1. Blood pressure profile collected over 24 hours following doses of 2.5 mg enalapril or 2.5 mg lisinopril. DBP = diastolic blood pressure; SBP = systolic blood pressure.

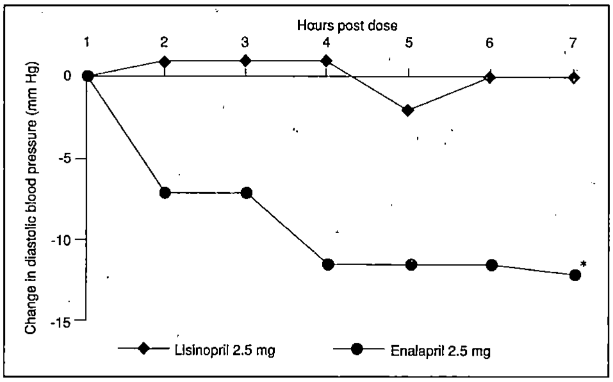

FIGURE 2. Treatment differences during time band 1 for diastolic blood pressure (arithmetic means). n = 7 patients per group. *p = 0.03

after administration.[6] By contrast, lisinopril undergoes no metabolism but is only slowly absorbed, reaching peak blood levels at 7 hours.[6] Both drugs have a long duration of action.[8]

A recent report[9] has suggested that ACE inhibitors may differ in their first dose hypotensive effects. Perindopril appears to have little effect on blood pressure at the first-dose compared with a marked effect produced by enalapril. There is the possibility that further decreases in blood pressures would have been observed had not the effects of sleep masked the effects of the ACE inhibitors in the second time band. The absence of any effect of the second dose of medication on blood pressure could be due to 2 possible causes: (1) both drugs were having an optimum effect on blood pressure when the second dose was given, or (2) any effect of the second dose may have been masked by the use of the first hour after this second dose as the baseline against which the effects of this second dose were compared.

At the present time, there are no internationally agreed standards for the analysis and interpretation of data from ambulatory blood pressure monitoring. Blood pressure values measured in the sitting position immediately before treatment may not be representative of untreated ambulatory blood pressure. Ambulatory blood pressure, measured in the first hour after administration may, on the other hand, be more appropriate, but could be influenced by any early effects of drug action. However, because neither drug used in this study is absorbed very rapidly, this may be unimportant.

It is possible that a decrease in blood pressure is a problem restricted principally to the first dose and that the majority of patients with mild-to-moderate heart failure are able adequately to compensate for the effects of ACE inhibition. Larger scale studies with ambulatory monitoring are clearly needed and ideally would incorporate a 24-hour recording of blood pressure on placebo before starting treatment, as well as ambulatory monitoring after the first dose. However, 48 hours of monitoring may prove too irksome for elderly heart failure patients.

In conclusion, in this small study, the first dose of enalapril appeared to produce a more pronounced early decrease in blood pressure than did lisinopril, perhaps reflecting differences in their rates of absorption and onset of action.

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Results of the Treatment Trial of the Studies of Left Ventricular Dysfunction (SOLVD)

Hubert Pouleur, MD, for the SOLVD Investigators

The primary objective of the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial was to determine if long-term mortality could be reduced by treatment with an angiotensin-converting enzyme (ACE) inhibitor, namely, enalapril, in patients with left ventricular dysfunction (resting ejection fraction $\leq 35\%$) and a history of overt congestive heart failure (CHF) treated concomitantly with conventional therapy. The secondary aims were to assess the effect of treatment on hospitalization for CHF and on mortality by cause.

METHODS

The SOLVD study was double-blind, randomized, and placebo controlled. This was a multinational study with 23 centers, mainly in the United States, but also in Canada and Belgium. Patients with CHF (aged 21–80 years) were eligible for the study if they had an ejection fraction $\leq 35\%$ and were not currently taking an ACE inhibitor as part of their conventional therapy. Exclusion criteria were acute ischemia, including myocardial infarction during the previous month, unstable angina, or any other disease that might substantially shorten survival or impede participation in a long-term study. The methods have been reported in detail elsewhere.[1]

All eligible patients participated in a prerandomization run-in. Patients received 2.5 mg enalapril twice daily for 2–7 days. Any patients exhibiting noncompliance or side effects were excluded at this stage. All patients were then given placebo for 14–17 days, and patients whose medical condition worsened or who were unable to comply with the regimen were identified and excluded from the study. At the end of this run-in phase, patients classified as having overt CHF were enrolled in the treatment trial and randomized to placebo or enalapril. The dose was increased, according to renal function and tolerance, to a target dose of 10 mg twice daily. Baseline patient characteristics are shown in Table I.

RESULTS

This study demonstrated a clinically important and significant reduction in mortality and hospitalizations for CHF over a 4-year period in patients treated with an ACE inhibitor in addition to conventional therapy.[1] At the end of the study, there were 510 deaths in the placebo group (39.7%) compared with 452 deaths (35.2%) in the enalapril group, a 16% reduction of risk in the intervention group ($p = 0.0036$). This benefit was mainly due to a 22% reduction in the risk of dying from progressive pump failure ($p < 0.0045$). There was little apparent effect on sudden deaths or deaths from arrhythmia (Figure 1). Overall, the total number of hospitalizations and the number of patients hospitalized were reduced significantly ($p < 0.001$). Analysis of combined cardiac deaths and the number of hospitalizations for worsening heart failure showed a 26% risk reduction with enalapril.

Most patients reported apparent side effects at some time during the study (87% with enalapril vs 82% with placebo). As shown in Table II, adverse effects related to hypotension (i.e., dizziness or fainting) occurred more frequently with enalapril ($p < 0.001$). A higher incidence of coughing

TABLE I Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial: Baseline Patient Characteristics

Characteristic	Placebo % (n = 1,284)	Enalapril % (n = 1,285)
Age (yr)	61.0	60.7
Qualifying EF	24.9	24.8
Males	79.8	80.9
Ischemic etiology	72.1	70.2
NYHA		
Class I	10.5	11.4
Class II	56.6	56.8
Class III	30.7	30.1
Class IV	1.9	1.5
CT ratio > 50%	55.6	57.6

CT: cardiothoracic; EF = ejection fraction; NYHA = New York Heart Assocation. Adapted with permission from *N Engl J Med*.[1]

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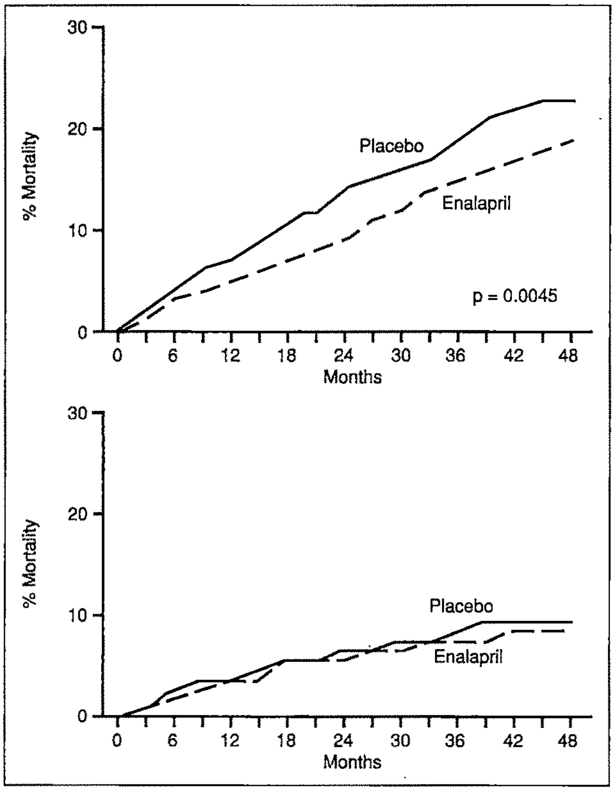

FIGURE 1. Mortality due to progressive heart failure (*upper panel*) (p = 0.0045) and presumed to be due to an arrhythmia but not preceded by worsening congestive heart failure (*lower panel*) (p = not significant). Reprinted with permission from *N Engl J Med*.[1]

($p < 0.001$), serum creatinine levels >2 mg/dL, and hyperkalemia >5.5 mEq/liter was also noted in the enalapril group. There was no excess of angioedema. These events seldom required discontinuation of the study drug, but rather dosage adjustment of both the study drug and concomitant medications.

DISCUSSION

The overall results of this trial appear to be consistent with the results of other studies of the benefit of ACE inhibitor therapy in CHF.[2,3] Indeed these studies suggest that ACE inhibitors are the vasodilators of choice in the management of this condition.[4] The reductions in deaths and rates of hospitalization are probably related to the observed improvements in pump function,[5] although the exact mechanism underlying the beneficial action of this class of drugs remains to be determined.

TABLE II Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial: Adverse Effects Reported at Any Postrandomization Visit

Adverse Effect	Enalapril (%)	Placebo (%)	p Value
Dizziness/fainting	57.2	50.4	<0.001
Coughing	35.0	30.2	<0.001
Angioneurotic edema	3.4	3.8	NS
Serum creatinine (> 2 mg/dL)	10.7	7.7	<0.01
Serum potassium (> 5.5 mEq/liter)	6.4	2.5	<0.01

NS = difference not significant.
Adapted with permission from *N Engl J Med*.[1]

Until now, most regulatory authorities have only recommended the addition of an ACE inhibitor to CHF therapy when the patient could not be stabilized with conventional therapy. However, the SOLVD treatment trial data indicate that ACE inhibitors should be introduced earlier, preferably at the time of diagnosis of CHF. Indeed, for the CHF population defined in the SOLVD trial, there is compelling evidence that delaying this treatment is keeping these patients under increased cardiovascular risk. This is also true for the patients who appear to be in a stable clinical condition (class I or II) with conventional therapy. The SOLVD investigators have calculated that treating 1,000 patients with an ACE inhibitor in conjunction with conventional therapy for 3 years could prevent 50 premature deaths and 350 hospitalizations. Therefore, in terms of cost and quality of life, the benefit of the early use of ACE inhibitors in the management of heart failure appears to be substantial.

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Comparison of the First-Dose Effect of Captopril and Lisinopril in Heart Failure

Karl J. Osterziel, MD, Markus Karr, MD, Christopher Busch, PhD, and Rainer Dietz, MD

Symptomatic hypotension after the first dose of angiotensin-converting enzyme (ACE) inhibitors is frequently observed in patients with heart failure,[1–3] and several risk factors, such as intensive diuretic therapy or hyponatremia, have been identified.[4] A common feature is that all risk factors stimulate the renin–angiotensin system (RAS).[4] Because the RAS is stimulated more frequently and/or to a greater extent in severe heart failure compared with mild or moderate heart failure,[5] hypotensive reactions are more frequent and the severity of hypotensive reactions after ACE inhibition is dependent on the dose of the ACE inhibitor used.[2] Further, the plasma half-life of the respective ACE inhibitor may influence the duration of the decrease in blood pressure.[6]

The incidence of symptomatic hypotension after the first dose can be reduced when small doses of ACE inhibitors are used. For instance, during the first few days of therapy with a starting dose of 2.5 mg enalapril twice daily, only 2.2% of patients with mild-to-moderate heart failure developed symptomatic hypotension,[3] and the rate of withdrawal due to symptomatic hypotension decreased from 11.8% to 3.2% in patients with severe heart failure considered at high risk to develop hypotension.[2] However, when assessing the effect of ACE inhibitors on blood pressure, circadian blood pressure variations were rarely taken into consideration. It was, therefore, the aim of this study to evaluate the blood pressure response to the first dose of 2 ACE inhibitors with different plasma half-lives (captopril and lisinopril) by comparing the 24-hour blood pressure profile before and on the first day of ACE inhibition in patients with mild-to-moderate heart failure.

METHODS

Forty patients with stable heart failure due to either dilated cardiomyopathy or coronary artery disease were examined (Table I). Concomitant therapy remained constant. Captopril 6.25 mg was given to 17 patients or 12.5 mg to 7 patients at 12:00–1:00 P.M. and the remaining 16 patients received 2.5 mg lisinopril at 10:00 A.M. The different times for the first dose was chosen in order to obtain the maximal effect of each drug at the same time of day. Both groups were comparable with respect to the etiology and severity of heart failure and concomitant medication (Table I).

The 24-hour blood pressure and heart rate rhythms were evaluated on the day preceding and on the day of administration of the first dose of an ACE inhibitor with a portable monitor (Spacelab

TABLE I Characteristics of the 2 Groups of Patients with Heart Failure

	Captopril (n = 24)	Lisinopril (n = 16)	p Value
NYHA classification (II/III/IV)	14/9/1	9/5/2	NS
Etiology:			
Ischemic CMP	13	6	NS
Dilated CMP	11	10	NS
Age (years)	58 ± 2	62 ± 2	NS
Height (m)	1.69 ± 0.02	1.71 ± 0.03	NS
Weight (kg)	68 ± 3	79 ± 3	0.01
Gender (M/F)	17/7	11/5	NS
Medication:			
Digitalis	4	7	NS
Diuretics	22	13	NS
Potassium supplement or potassium-sparing diuretics	21	8	NS
Nitrates or molsidomine	9	6	NS
β Blockers	9	1	0.05
Antiarrhythmic drugs	2	4	NS
NSAIDs	5	4	NS

CMP = cardiomyopathy; NSAIDs = nonsteroidal anti-inflammatory drugs; NYHA = functional classification according to the New York Heart Association.

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90 202) by the oscillometric method. Measurements were taken every 20 minutes from 6:00 A.M. to 10:00 P.M. and every hour from 10:00 P.M. to 6:00 A.M. Average hourly blood pressure data were used for further evaluation. The blood pressure rhythm was calculated for each patient as an optimized curve consisting of 3 sinus functions with periods of 8, 12, and 24 hours. The decay of the first-dose effect was calculated by fitting an exponential curve to the blood pressure values. The variables are expressed as mean ± standard deviation. A p value < 0.05 was considered significant.

RESULTS

Both groups showed a similar circadian blood pressure rhythm before therapy with ACE inhibitors (Figure 1). The average 24-hour systolic, diastolic, and mean blood pressures in the captopril group were not significantly different from the values in the lisinopril group (Figure 1). The maximal differences of blood pressure during the 24-hour period (amplitudes) were used as a measure of day/night rhythms. Both groups showed a similar decrease of blood pressure during the night, with amplitudes that were not significantly different between groups. The mean heart rate was also not significantly different between the captopril and lisinopril groups (74 ± 16 liters/min for captopril and 74 ± 15 liters/min for lisinopril). Therefore, both groups were well balanced. No patient experienced symptomatic hypotension after the first dose of captopril or lisinopril. The drug effect on blood pressure was evaluated by subtracting the hourly blood pressures after ACE inhibition from the hourly blood pressures at the same time on the day before ACE inhibition. For the

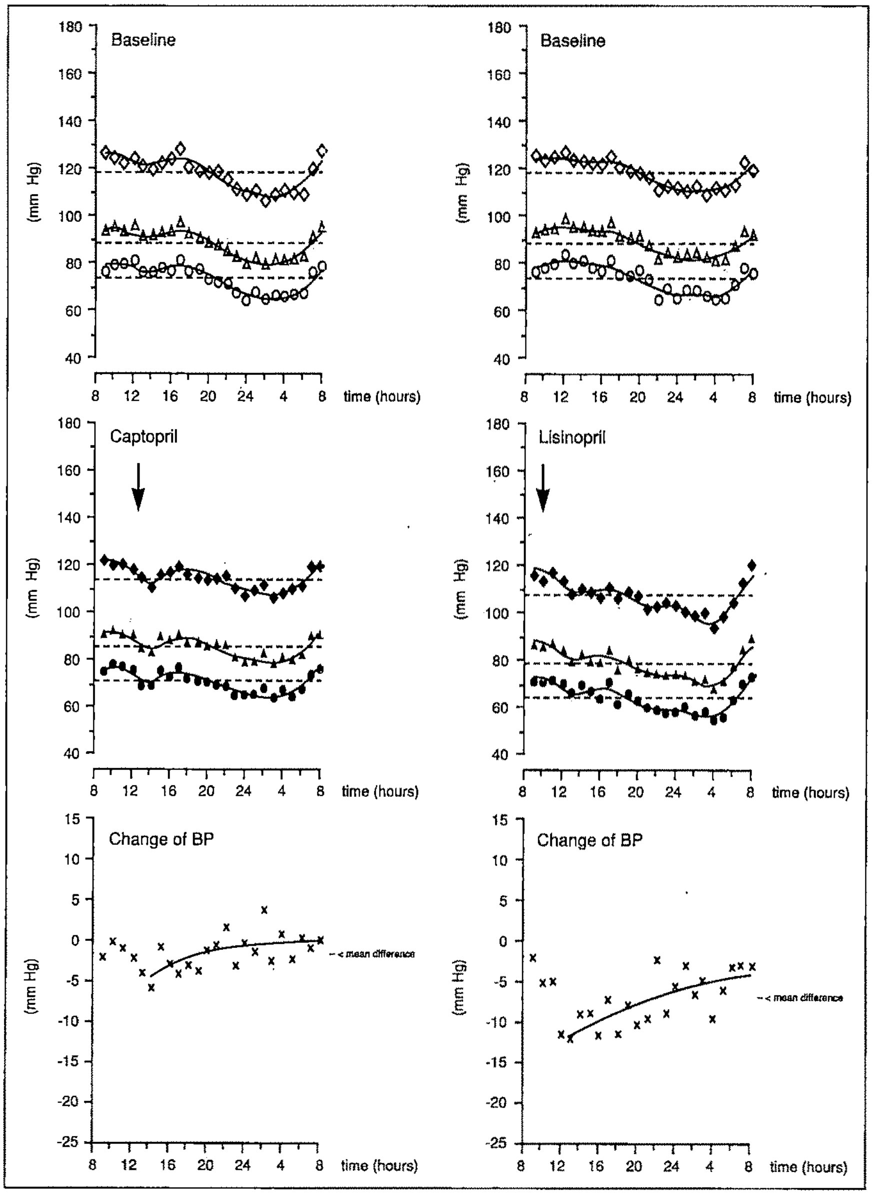

FIGURE 1. The 24-hour blood pressure measurements at baseline (*open symbols*) and on the day of the first-dose application (*closed symbols*) of captopril or lisinopril. The time of the first-dose application is shown by arrows. The bottom figure shows the differences (day 1 to day 0) in mean blood pressure and the calculated curves of decay of the effect.

whole captopril group, the maximal decrease in mean blood pressure of 6.5 mm Hg occurred at 2:00 P.M. The half-life of decay of the decrease in blood pressure was 5.2 hours. The maximal decrease in blood pressure (12.1 mm Hg) occurred at 1:00 P.M. in the lisinopril group. The decrease in blood pressure was long lasting, with a half-life of decay of 12.8 hours. The maximal response to captopril or lisinopril was not observed at the same time of day. The lowest values for the captopril group were observed at 1:00 (n = 6), 2:00 (n = 9), or 3:00 P.M. (n = 9) so that the effect of captopril would be underestimated when the hourly means of the whole group were used for evaluation. In contrast, the onset of the effect with lisinopril was slow and near maximal effects were obtained in most patients at 1:00 P.M. In order to compare maximal drug effects, the maximal decrease in mean blood pressure was calculated for each patient and the means were compared between the 2 groups. Blood pressure decreased significantly in both groups but the maximal blood pressure responses were not significantly different between the captopril and lisinopril groups (Figure 2). Because of the longer duration of action, the 24-hour mean heart rate decreased slightly with lisinopril, but remained unchanged with captopril.

DISCUSSION

The incidence of symptomatic hypotension is low in patients with mild-to-moderate heart failure.[3,6] Most patients in this study were in stable mild-to-moderate heart failure and therefore at low risk of developing serious hypotension after the first dose of ACE inhibitors. With the use of low doses of captopril or lisinopril, none of our patients exhibited symptoms of hypotension. When the circadian variation of blood pressure is considered, the maximal blood pressure response to the first dose of 8.1 ± 3.0 mg captopril was not significantly different from the maximal decrease after 2.5 mg lisinopril (10.9 ± 2.2 vs 11.0 ± 2.7 mm Hg). The maximal decreases in blood pressure were similar when higher initial doses of captopril or lisinopril were used in a comparable group of patients.[6] Because of the different plasma half-lives, the duration of the decrease in blood pressure was longer after the first dose of lisinopril. Considering the magnitude and the duration of the first-dose effect, an even smaller initial dose of captopril or lisinopril may be desirable to minimize unwanted first-dose effects in patients who are at high risk of developing symptomatic hypotension.

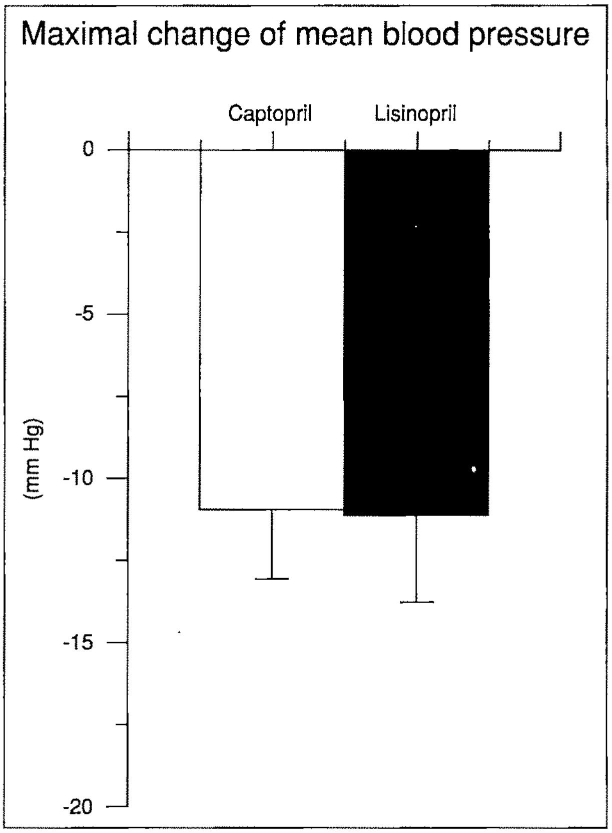

FIGURE 2. For each patient, the maximal decrease of mean blood pressure was calculated by subtracting the hourly means at baseline and on the first day of angiotensin-converting enzyme (ACE) inhibition. The means of the maximal blood pressure changes after the first dose of captopril and lisinopril are shown.

CONCLUSION

Small doses of captopril or lisinopril lead to a significant and comparable maximal blood pressure decrease in patients with mild-to-moderate heart failure. However, the duration of the effect after lisinopril was longer than after captopril.

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Effects of Hydrochlorothiazide, Amiloride, and Lisinopril on the Metabolic, Hemodynamic, and Electrocardiographic Responses to Increased Plasma Epinephrine

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In the treatment of cardiovascular disease, such as hypertension and heart failure, minor metabolic side effects of the long-term pharmacologic treatment might be of importance. Thus, diuretics may induce a potentially arrhythmogenic hypokalemia[1] and have negative effects on the glucose metabolism, and both diuretics and β blockers may have adverse effects on blood lipid levels[2] that might increase the risk of coronary artery disease, despite the benefits provided by these drugs' antihypertensive actions. In experimental settings, an infusion of epinephrine given at a rate to obtain serum concentrations comparable to those seen in acute myocardial infarction has profound metabolic and electrocardiographic effects that are known to facilitate the development of malignant ventricular arrhythmias.[3] These effects of epinephrine may be aggravated by some drugs commonly prescribed in cardiovascular disorders.[4] This study investigated the effects of pretreatment with hydrochlorothiazide, amiloride, and lisinopril on the response to an epinephrine infusion.

METHODS

On 4 separate occasions, each separated by ≥4 weeks, 12 healthy male volunteers, aged 23–38 years (mean 28.8), received an infusion of epinephrine (0.05 μg/min/kg body weight over 120 minutes). The infusion was given in a cannulated antecubital vein with the volunteer in the supine position, and all infusions were started at 1:00 P.M. From an indwelling catheter in the opposite arm, blood was drawn 15 minutes before epinephrine infusion, at the start of epinephrine infusion, and subsequently at 15-minute intervals, until 30 minutes after the infusion. The following serum values were analyzed: potassium, magnesium, calcium, phosphate, urate, albumin, creatinine, and blood glucose. An electrocardiographic recording was made during the infusion and for the following 30 minutes. The recording was analyzed for heart rate, T-wave amplitude, QRS duration, and QT interval. Systolic and diastolic (phase V) blood pressures were also determined.

Prior to the epinephrine infusion, the volunteers were pretreated in random order for 14 days with: (1) placebo, (2) hydrochlorothiazide (HCTZ) 50 mg daily, (3) amiloride 10 mg daily, and (4) lisinopril 20 mg daily. Each volunteer received all of the pretreatments (Latin square design).

The results were expressed as mean ± standard deviation. For statistical analysis, a multivariate analysis of variance for repeated measurements (MANOVA) was used with time during epinephrine infusion and the various pretreatments as within-subject factors.

RESULTS

The results in Table I show that the epinephrine induced a decrease in serum potassium, calcium, and magnesium that was similar for all pretreatment groups. Because of the potassium-lowering effect of HCTZ, determined before the start of the epinephrine infusion, the lowest serum potassium (2.98 ± 0.37) was seen after pretreatment with HCTZ. A significant interaction was found between the effect of the epinephrine and the various pretreatments on blood glucose, with a greater increase in blood glucose during epinephrine infusion after HCTZ than after placebo. After pretreatment with lisinopril, blood glucose increased less during epinephrine infusion than after the other pretreatments, although the difference was not statistically significant when compared with placebo. However, when lisinopril was compared with the diuretics, it was found that both HCTZ ($p < 0.001$) and amiloride ($p < 0.01$) accentuated

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TABLE I Change in Metabolic Parameters Just Before and After 120 minutes of Epinephrine

	Epinephrine Infusion	Placebo	Hydrochlorothiazide	Amiloride	Lisinopril
Serum potassium (mmol/liter)	Before	4.03 ± 0.21	3.51 ± 0.33	4.13 ± 0.38	4.14 ± 0.23
	After	3.39 ± 0.31	2.98 ± 0.37	3.52 ± 0.34	3.53 ± 0.24
Serum magnesium (mmol/liter)	Before	0.847 ± 0.07	0.845 ± 0.08	0.837 ± 0.06	0.839 ± 0.06
	After	0.784 ± 0.05	0.787 ± 0.08	0.773 ± 0.05	0.783 ± 0.06
Serum calcium (mmol/liter)	Before	2.38 ± 0.07	2.44 ± 0.08	2.40 ± 0.11	2.39 ± 0.11
	After	2.31 ± 0.11	2.33 ± 0.11	2.28 ± 0.08	2.31 ± 0.09
Serum phosphate (mmol/liter)	Before	1.16 ± 0.16	1.16 ± 0.15	1.12 ± 0.16	1.08 ± 0.14
	After	0.92 ± 0.15	0.82 ± 0.16	0.96 ± 0.15	0.96 ± 0.13
Serum urate (μmol/liter)	Before	350.33 ± 43.79	428.08 ± 56.16	343.92 ± 40.42	360.83 ± 51.65
	After	348.67 ± 52.27	418.92 ± 60.50	340.42 ± 39.22	353.42 ± 48.86
Serum creatinine (μmol/liter)	Before	105.25 ± 19.92	105.75 ± 13.28	104.25 ± 8.44	100.00 ± 9.73
	After	112.25 ± 15.60	118.25 ± 15.18	113.08 ± 13.31	111.92 ± 11.95
Serum albumin (g/liter)	Before	39.92 ± 1.88	41.58 ± 2.07	40.25 ± 1.82	40.25 ± 2.73
	After	39.67 ± 2.54	39.75 ± 1.55	39.00 ± 1.48	39.42 ± 2.54
Blood glucose (mmol/liter)	Before	4.58 ± 0.68	4.51 ± 0.70	4.58 ± 0.76	4.60 ± 0.89
	After	8.56 ± 1.88	9.44 ± 2.50	9.44 ± 1.62	8.23 ± 1.60

the epinephrine-induced increase in blood glucose. Lisinopril pretreatment also significantly modified the epinephrine-induced changes in serum phosphate ($p < 0.001$), resulting in a significantly smaller decrease in serum phosphate during epinephrine infusion than after pretreatment with placebo or HCTZ.

Epinephrine caused significant increases in heart rate and systolic blood pressure and a decrease in diastolic blood pressure. These effects of epinephrine were not significantly modified by the various pretreatments.

During epinephrine infusion, significant prolongations of the QRS and the QT_c durations and a flattening of the T-wave amplitude were seen, but these responses were not significantly modified by the pretreatments. On the other hand, the QT_c interval at baseline before epinephrine infusion was significantly prolonged after HCTZ compared with placebo, and also after HCTZ, the QRS duration was significantly longer before epinephrine than after pretreatment with amiloride or lisinopril.

CONCLUSION

These results, although they are obtained in normal subjects in an experimental setting, suggest that angiotensin-converting enzyme (ACE) inhibitors may have certain metabolic advantages over diuretics, and they might lend support to use of ACE inhibitors as first-line drugs in mild hypertension and at an early stage in heart failure.

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Study of the Safety and Efficacy of ACE Inhibitors and Their Effects on 24-Hour Electrocardiographic Monitoring in the Treatment of Moderate-to-Severe Heart Failure: An Interim Analysis

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Since their introduction, angiotensin-converting enzyme (ACE) inhibitors have become a significant new treatment for congestive heart failure (CHF) and a considerable amount of evidence has been accumulated to indicate that ACE inhibitors can reduce the frequency of arrhythmias in patients with CHF. However, the mechanism by which this effect on arrhythmias is achieved is not yet clear. The following describes an interim analysis of a study comparing the efficacy and tolerability of lisinopril and enalapril in the treatment of moderate-to-severe CHF. The first 156 patients who completed or withdrew from the study are included with treatment codes unbroken. The emphasis of this interim analysis is placed on describing the patient population and making comparisons over the course of the study. The target for recruitment to the study will be 250 patients and the full results are expected mid-1992.

METHODS

Patients >18 years of age with CHF in New York Heart Association (NYHA) class III or IV confirmed by clinical signs and symptoms and a left ventricular ejection fraction at rest of <35% were recruited into the study after giving signed informed consent (Table I). Patients were excluded from the study if they had uncontrolled arrhythmias, including bigeminal rhythm, but were allowed into the study if they had been controlled on a regular dose of an antiarrhythmic agent for at least 4 weeks (8 weeks for amiodarone) prior to entry to the study. Patients were excluded from the study if they were unable to perform at least 1 minute of an exercise treadmill test or for any medical condition that in the opinion of the investigator rendered the patient unsuitable for the study.

This was a multicenter, double-blind, double-dummy, randomized, parallel-group comparison of the effects of lisinopril and enalapril in patients with moderate-to-severe CHF. The following baseline measurements were recorded: (1) exercise test performance, (2) left ventricular ejection fraction, (3) NYHA status, and (4) 24-hour Holter tape. After randomization, each patient received a 2.5 mg test dose of ACE inhibitor and was monitored for 6 hours. If no first-dose hypotension developed, the patient continued in the study on a 5 mg daily dose. At subsequent visits, the dose was increased incrementally to 20 mg daily unless the patient developed a systolic blood pressure of <90 mm Hg or showed signs of hypotension. Patients were reassessed in the hospital at 2, 4, 6, 12, 18, and 24 weeks (visit 9). At visit 9 the following were recorded: (1) exercise test performance, (2) left ventricular ejection fraction, (3) NYHA status, (4) adverse events, and (5) a second 24-hour Holter tape.

TABLE I Demographic Data

Sex	Male	122
	Female	34
Age (years)	Mean (SD)	62.1 (9.6)
	Minimum	24
	Maximum	78
NYHA status	Class III	125
	Class IV	31
LVEF (%)	Mean (SD)	21.3 (8.6)
No.	—	156

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

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TABLE II Efficacy and Safety

	Pretreatment (Visit 2)		Post-treatment (Visit 9)		(Visit 9 to Visit 2)			
	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	95% Confidence Interval	p Value
LVEF (%)	21.3 (8.6)	156	25.9 (11.4)	115	5.0 (8.9)	115	3.4–6.6	<0.0001
Exercise duration (seconds)	407.8 (264.4)	151	574.4 (329.6)	112	128.6 (199.5)	108	90.6–166.6	<0.0001

LVEF = left ventricular ejection fraction; SD = standard deviation.

RESULTS

The data show that in patients with moderate-to-severe CHF, 6 months treatment with an ACE inhibitor (lisinopril or enalapril) improved left ventricular ejection fraction, exercise duration and NYHA status (Tables II and III). An improvement in left ventricular ejection fraction occurred in 70% and an improvement in NYHA status occurred in 71%. Of the 156 patients who have completed or withdrawn from the study so far, 71 had both pre- and post-treatment Holter tapes available for analysis. There were no clear changes in pre- and post-treatment values for the following arrhythmias: (1) unifocal ventricular ectopic count, (2) multifocal ventricular ectopic count, (3) sustained monomorphic ventricular tachycardia, or (4) sustained polymorphic ventricular tachycardia. Small improvements were seen in episodes of atrial fibrillation and nonsustained monomorphic and polymorphic ventricular tachycardia (Tables IV–VII).

CONCLUSION

From this preliminary analysis of the arrhythmias found in patients with moderate-to-severe heart failure treated with the ACE inhibitors lisinopril or enalapril, there is some suggestion that there may be a beneficial effect on atrial fibrillation and nonsustained monomorphic and polymorphic ventricular tachycardia. There appears to be little change in the other arrhythmias found in this population. There was no evidence of a deterioration in the number or type of arrhythmias.

It should be stressed that this is an initial inspection of the mean data which requires further confirmation when the full data are available. More detailed analysis can then be performed, and different treatment effects will be investigated at that time. Because this is an interim analysis, the number of withdrawals from the study represent an artificially high percentage (28%) of patient dropouts. In addition, since the analysis is based on the number of patients who have either completed or withdrawn from the study at a particular time, it does not take into account those patients still to

TABLE III Functional Heart Status

		NYHA Classification Post-Treatment (Visit 9)				
		Class I	Class II	Class III	Class IV	Total
NYHA classification pre-treatment	Class III	6	60	30	2	98
visit 2	Class IV	4	6	8	3	21
Total		10	66	38	5	119

NYHA = New York Heart Assocation.

TABLE IV Holter Monitoring: Number of Episodes of Atrial Flutter/Atrial Fibrillation

	Episodes	No.	%
Visit 2 (pretreatment)	0	100	83
	1	18	15
	2	2	2
Total		120	100
Visit 9 (post-treatment)	0	78	92
	1	7	8
	2	0	0
Total		85	100
Change from visit 2 to visit 9	−2	1	1
	−1	1	1
	0	69	97
Total		71	100

TABLE V Holter Monitoring: Nonsustained Monomorphic Ventricular Tachycardia

		Time (seconds)
Visit 2 (pretreatment)	Mean (SD)	15.6 (139.4)
	Median	0.0
	Minimum	0.0
	Maximum	1,525
	No.	120
Visit 9 (post-treatment)	Mean (SD)	2.5 (9.8)
	Median	0.0
	Minimum	0.0
	Maximum	79.8
	No.	85
Changes from visit 2 to visit 9*	Mean (SD)	−22.9 (181.5)
	Median	0.0
	Minimum	−1,525
	Maximum	67.8
	No.	71

*Defined as the assessment at visit 9 minus that at visit 2.
SD = standard deviation.

complete the study. Further, it may be the case that "good" patients completed the study and "bad" patients withdrew before completion, thus biasing the statistical tests comparing initial and final values performed in this interim analysis. A total of 44 patients withdrew; reasons for withdrawal were death (n = 11), adverse reactions (n = 32), and protocol violation (n = 1). Of those who did withdraw or died, 32 were NYHA class III, and 12 were NYHA class IV. In the final report a pragmatic intention-to-treat approach will be adopted to address this problem. Table VIII shows causes of death. None of the deaths were thought to be attributable to the trial medication.

The most common reported adverse reactions are given in Table IX. These appear to fit the standard profile for ACE inhibitors. This study was designed to look at the possible differences between lisinopril and enalapril in the treatment of moderate-to-severe CHF. The interim analysis has shown the positive benefits of ACE inhibitor therapy without looking at the differences between the ACE inhibitors used in the study. When the final analysis of the study is available, it will be interesting to see if there are any differences between the 2 different treatments.

TABLE VI Holter Monitoring: Nonsustained Polymorphic Ventricular Tachycardia (Episodes)

		Episodes
Visit 2 (pretreatment)	Mean (SD)	9.1 (69.1)
	Median	0.0
	Minimum	0.0
	Maximum	721
	No.	120
Visit 9 (post-treatment)	Mean (SD)	1.5 (6.2)
	Median	0.0
	Minimum	0.0
	Maximum	43
	No.	85
Change from visit 2 to visit 9*	Mean (SD)	−13.0 (83.6)
	Median	0.0
	Minimum	−678
	Maximum	4
	No.	71

*Defined as the assessment at visit 9 minus that at visit 2.
SD = standard deviation.

TABLE VII Holter Monitoring: Nonsustained Polymorphic Ventricular Tachycardia (Time [seconds])

		Time (seconds)
Visit 2 (pretreatment)	Mean (SD)	14.3 (118.5)
	Median	0.0
	Minimum	0.0
	Maximum	1,278
	No.	120
Visit 9 (post-treatment)	Mean (SD)	1.8 (7.9)
	Median	0.0
	Minimum	0.0
	Maximum	60.8
	No.	85
Change from visit 2 to visit 9*	Mean (SD)	−21.1 (146.1)
	Median	0.0
	Minimum	−1,217.2
	Maximum	6.4
	No.	71

*Defined as the assessment at visit 9 minus that at visit 2.
SD = standard deviation.

TABLE VIII Causes of Death

	No. Patients
Sudden death	4
Myocardial infarct	4
Coronary thrombosis	1
Cardiac failure/ischemic heart disease	1
Left ventricular failure	1

TABLE IX Most Common Reported Adverse Reactions

	No. Patients
Cough	38
Dizziness	32
Headache	12
Tiredness	9
Diarrhea	8
Postural effects	8
Blackouts	6
Lethargy	6
Nausea	6

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Effects of Lisinopril on Brain Atrial Natriuretic Factor in Uremic Rats

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Miklos Palkovits, MD, August Heidland, MD, and Friedrich C. Luft, MD

Atrial natriuretic factor (ANF) is a peptide hormone elaborated by the atria, which has potent renal, adrenal, and vascular actions on electrolyte homeostasis and blood pressure. Similar materials have been located at other sites, including the kidney and the brain. In the brain the most prominent group of ANF-containing neurons is found in the periventricular, preoptic, and hypothalamic areas adjacent to the anteroventral wall of the third ventricle. This area, which is also known as the AV3V region, is important in the regulation of both salt and water intake and blood pressure. Cell groups in this area contain ANF in high concentrations within the neuronal cell bodies, fibers, and nerve terminals. Previously, we examined the concentration of brain ANF in these and other brain areas in three different rat models of hypertension. Our observations suggested a role for ANF within the AV3V region in the regulation of salt and water homeostasis.

The peptide angiotensin II (ANG II) is also important in blood pressure regulation in both the periphery and the brain. To elucidate the relation between brain ANF and ANG II, we conducted investigations in rats subject to angiotensin-converting enzyme (ACE) inhibition. To magnify the potential interactions, the rats were subjected to reduced renal mass.

METHODS

The study was carried out on 28 male Wistar rats (240 g), which were divided into 3 experimental groups: controls, 5/6 nephrectomized rats, and 5/6 nephrectomized rats treated with the ACE inhibitor lisinopril (20 mg/kg) from day 7 to day 12. The 5/6 nephrectomy (NPX) was performed under pentobarbital anesthesia (60 mg/kg).

All rats were decapitated on day 12. This was followed by microdissection of the brain nuclei. Brain ANF concentrations were determined by radioimmunoassay with C terminal directed antiserum, which recognizes the specific polypeptide fragments of brain ANF with a cross-reactivity of 100% toward rat ANF (103–126) and of 88% toward rat ANF (102–126). Intra-assay variability is 8% and interassay variability is 14%.

RESULTS

As shown in Figure 1, 5/6 NPX resulted in increased systolic blood pressure ($p < 0.001$) and caused proteinuria ($p < 0.001$), both of which were reduced to normal levels by lisinopril ($p < 0.001$). Treatment with lisinopril also reduced circulating ANF levels ($p < 0.001$), but 5/6 NPX increased drinking ($p < 0.01$) and urine volume ($p < 0.001$). These were also reduced, but not to normal levels, by lisinopril, and 5/6 NPX resulted in slightly decreased plasma sodium ($p < 0.05$), but this was restored to normal levels by lisinopril.

As shown in Figure 2, 5/6 NPX caused increased ANF levels in the periventricular preoptic nucleus ($p < 0.05$), the perifornical nucleus ($p < 0.05$) and the arcuate nucleus ($p < 0.001$), which were restored to control levels by lisinopril. Also, 5/6 NPX caused increased ANF concentrations in the periventricular hypothalamic nucleus ($p < 0.05$), the paraventricular hypothalamic nucleus ($p < 0.01$) and the dorsal raphe nucleus ($p < 0.05$). However, these values were not influenced by lisinopril (Figure 2).

CONCLUSION

To test the effect of ANG II converting-enzyme inhibition on brain ANF values, we employed a 5/6 NPX rat model that relied on ligation of renal branch arteries.[1] Reduced renal mass resulted in increased blood pressure, increased urine volume, and increased drinking. There was also a decrease in plasma sodium. Lisinopril lowered blood pressure to control values, decreased urine volume and

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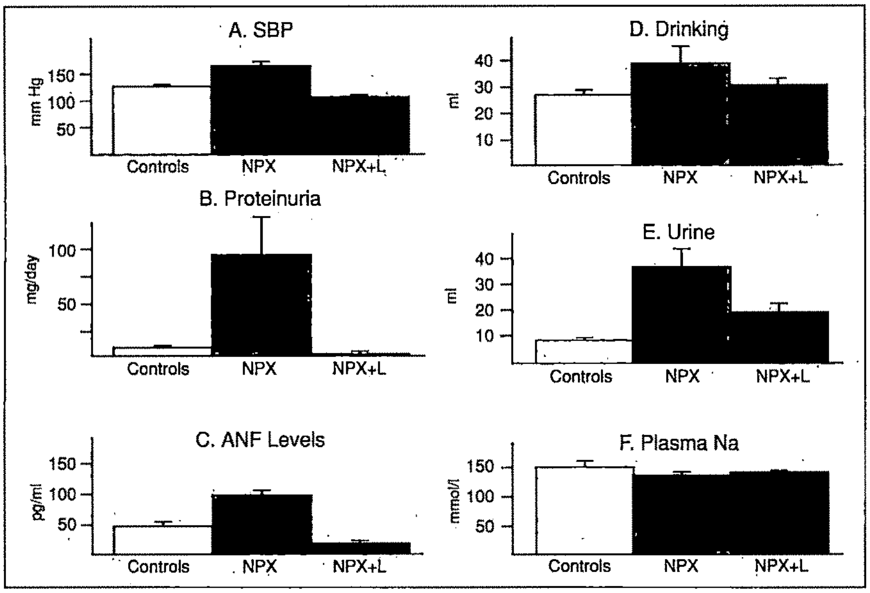

FIGURE 1. Effect of 5/6 nephrectomy (NPX) and subsequent lisinopril (L) treatment on key physiologic parameters. ANF = atrial natriuretic factor; Na = sodium; SBP = systolic blood pressure.

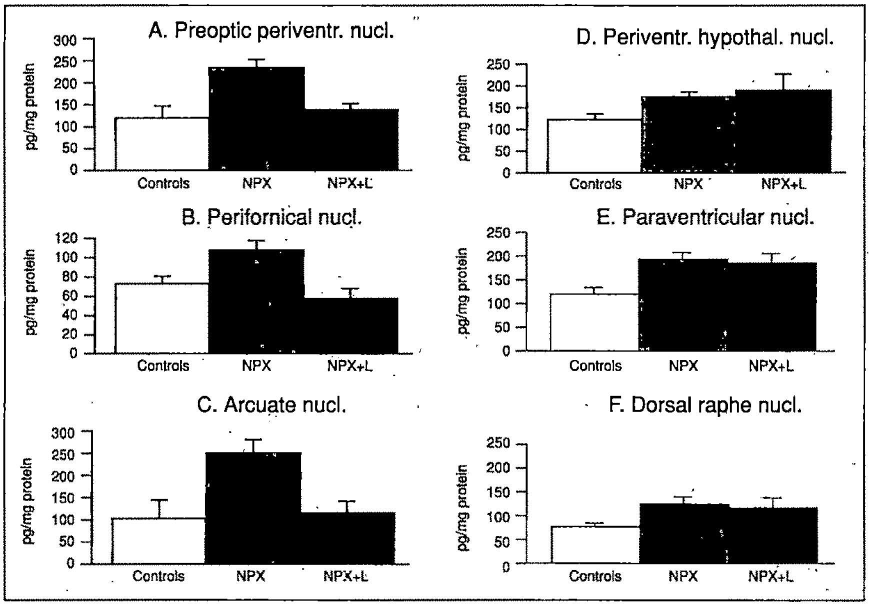

FIGURE 2. Atrial natriuretic factor concentrations in selected brain areas. L = lisinopril; NPX = 5/6 nephrectomy; nucl. = nucleus; periventr. = periventricular.

drinking, and normalized plasma sodium values. Plasma ANF values decreased sharply with lisinopril.

Reduced renal mass also resulted in an increase in ANF values in 6 brain areas. In 3 of these brain areas, the periventricular preoptic nucleus, the arcuate nucleus, and the perifornical nucleus, lisinopril treatment resulted in a decrease in brain ANF values to control levels. In the 3 other brain areas, however, lisinopril caused no reduction in the increased ANF concentrations, suggesting that the ANF increases in these areas were not dependent on ANG-II related mechanisms.

These results suggest that in the AV3V and related nuclei, brain ANF may play a role in drinking behavior and sodium and water homeostasis. Further, ANF in these areas may be influenced by ANG II-related mechanisms.

These preliminary observations allow only a crude view of the inter-relations between ANF and ANG II in the brain and in the peripheral circulation. However, they suggest that further study of the AV3V region, using more sensitive techniques, may be fruitful.

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Effect of Captopril and Lisinopril on Circadian Blood Pressure Rhythm and Renal Function in Mild-to-Moderate Heart Failure

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Symptomatic arterial hypotension and functional renal impairment are important side effects in patients with heart failure during therapy with angiotensin-converting enzyme (ACE) inhibitors.[1,2] Even after identification of high-risk patients and reduction of the initial dose of enalapril, symptomatic hypotension occurred in 3.2% of patients with severe heart failure (New York Heart Association [NYHA] class IV).[1] Minor functional renal impairment during therapy with ACE inhibitors can be found in 10–14% of patients with heart failure.[2,3]

Differences in plasma half-life may be responsible for observed differences in hemodynamic alterations by ACE inhibitors.[3,4] With short-acting ACE inhibitors, periodic increases and decreases in blood pressure were reported, whereas blood pressure remained at nearly constant low levels during therapy with a long-acting ACE inhibitor.[4] The degree of renal impairment is thought to be caused by the length of time the blood pressure is below the renal autoregulatory threshold.[4] However, most studies on the effects of ACE inhibition on blood pressure and renal function have only measured arterial pressure for a few hours.

To test the hypothesis that long-acting ACE inhibitors lead to a continuous decrease in arterial pressure, whereas short-acting ACE inhibitors allow recovery of blood pressure between dosing, the influence of 2 different ACE inhibitors on the 24-hour blood pressure profile was determined. Circadian blood pressure rhythm and renal function were evaluated before and after the titration period (5 days) with captopril or lisinopril.

METHODS

Twenty-eight hospitalized patients (25 men and 3 women) with heart failure (NYHA class II–IV) were examined. The diagnosis was confirmed in every patient by right and left heart catheterization and selective coronary angiography. All patients were randomized for additional therapy with either captopril or lisinopril. The 2 groups did not differ in etiology, severity of heart failure, and concomitant medication, with the exception that 5 patients in the captopril group received low doses of β blockers (Table I). One patient in each group had diabetes mellitus. During the titration period with the 2 ACE inhibitors, only changes in the diuretic therapy according to clinical needs were allowed. One patient in the captopril group previously not on diuretics received a thiazide diuretic. The diuretic dosage was reduced in 1 patient and increased in 1 patient in the lisinopril group.

Blood pressure and heart rate were determined by the oscillometric method (Spacelab monitor, model 90 202) before and on day 5 of therapy with either captopril or lisinopril. The blood pressure values obtained by this method are reproducible and show a close correlation with intra-arterial measured values.[5] Blood pressure and heart rate were recorded every 20 minutes from 6:00 A.M. to 10:00 P.M. and every 60 minutes from 10:00 P.M. to 6:00 A.M.. Serum electrolytes, serum creatinine, and urine creatinine were measured by an autoanalyzer method and plasma renin activity was determined at 11:00 P.M. by a radioimmunoassay.

The average hourly means of blood pressure and heart rate were used to analyze for daily variations. Within groups, the alterations of blood pressure and heart rate over time were compared by analysis of variance (ANOVA). In addition, rhythm analysis was performed by non-linear fitting of the hourly data to cosine function with the PHARMFIT program.[6] The fitting procedure is based on the Marquardt–Levenberg algorithm. This is performed by searching the minimum difference in the sum of squares between measured and calculated values of the dependent variable (blood pressure or heart rate). Data were fitted to a 24-hour period and to a 24-hour period overlap-

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TABLE I Characteristics of the 2 Groups of Patients with Congestive Heart Failure

	Captopril (n = 15)	Lisinopril (n = 13)	p Value
NYHA classification	2.8 ± 0.1	2.8 ± 0.2	NS
Etiology			
Ischemic CMP	5	4	NS
Dilated CMP	10	9	NS
Age (yr)	60 ± 3	62 ± 3	NS
Height (m)	1.69 ± 0.02	1.73 ± 0.02	NS
Weight (kg)	67 ± 3	84 ± 4	0.01
Gender	13/2	12/1	NS
Medication			
Digitalis	2	7	NS
Diuretics	12	10	NS
Potassium supplement	5	4	NS
Nitrates	4	2	NS
Molsidomine	3	3	NS
β blockers	5	0	0.05
Calcium antagonists	2	1	NS
Mexiletine	1	0	NS
Quinidine	0	2	NS
NSAIDs	2	2	NS

CMP = cardiomyopathy; NS = difference not significant; NSAIDs = nonsteroidal anti-inflammatory drugs; NYHA = functional classification according to the New York Heart Association.

ping with its first harmonics (12 hours); improvement of fit was tested. The mesor (rhythm-adjusted mean), acrophase (peak time of rhythm), and amplitude before and after ACE inhibitor treatment were compared by *t*-test. Differences in other variables were evaluated by the Wilcoxon signed rank test or by the Mann-Whitney U test. The correlation coefficient of linear regressions was calculated by the method of Pearson.

RESULTS

Fifteen patients received captopril 3 times daily at 8:00 A.M., 12:00 and 5:00 P.M. and 13 patients were treated with lisinopril once daily at 8:00 A.M. The mean daily doses were 41 ± 4 mg captopril and 9.6 ± 0.4 mg lisinopril. Before ACE inhibition, both groups showed a similar circadian blood pressure rhythm with highest values in the morning, a slight decrease in blood pressure in the early afternoon, a second peak at about 6:00 P.M. and a sustained decrease in blood pressure during the night (Figure 1; Table II). The profiles of the 24-hour heart rate showed a less consistent but similar pattern to the blood pressure curves (Figure 2; Table II). In the captopril group alterations in the circadian heart rate pattern by the concomitant β blocker therapy of 5 patients cannot be excluded. Therapy with captopril or lisinopril led to a significant decrease in the mesor of systolic and diastolic blood pressure (Table II). There was a tendency to greater blood pressure alterations by lisinopril in comparison to captopril. A slight decrease in the amplitudes of the dominant 24-hour fit was observed in both groups (Table II), whereas the amplitudes of the 12-hour fit did not change. Therefore, circadian blood pressure rhythm before and during ACE inhibition was not significantly different.

The increase in serum potassium in the captopril group was most likely due to a greater number of patients receiving potassium-sparing diuretics (6 vs 3 patients). Treatment with ACE inhibitors did not change serum creatinine. Captopril did not change creatinine clearance but lisinopril therapy tended to reduce creatinine clearance ($p < 0.11$; Table III). Plasma renin activity increased in the captopril group from 4.7 ± 1.3 to 16.3 ± 4.6 ng Al/mL/hr ($p < 0.01$) and in the lisinopril group from 3.8 ± 0.8 to 23.6 ± 4.9 ng Al/mL/hr ($p < 0.01$). There were no significant differences

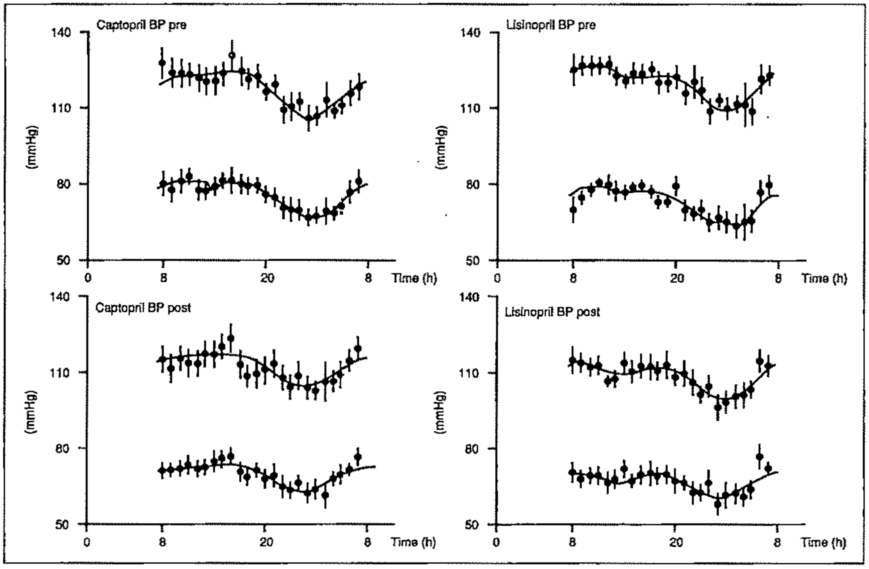

FIGURE 1. Circadian rhythm of systolic and diastolic blood pressure (BP) in mild-to-moderate heart failure before (pre) and during (post, 5th day) therapy with captopril or lisinopril. Captopril was applied at 8:00 A.M., 12:00, and 5:00 P.M. and lisinopril in a single dose at 8:00 A.M. daily. Shown are mean hourly values ± standard deviation of the mean of 15 captopril and 13 lisinopril patients.

TABLE II Circadian Rhythm of Blood Pressure and Heart Rate Before and During Angiotensin-Converting Enzyme Inhibition

	Mesor (mean ± SD)	Amplitude (mean ± SD)		Acrophase (hours ± SD)		% Rhythm	Significance	
		24 hours	12 hours	24 hours	12 hours		Cosinor (p)	ANOVA (p)
Captopril								
Heart rate (beats/min)								
Pretherapy	76.4 ± 0.9	6.2 ± 3.1	3.6 ± 1.3	14.4 ± 0.8	8.0 ± 0.7	57.4*	0.014	NS
During therapy	76.8 ± 0.5	5.6 ± 0.7	3.4 ± 0.7	13.5 ± 0.4	9.0 ± 0.4	82.7*	<0.0001	NS
BP systolic (mm Hg)								
Pretherapy	117.8 ± 0.7	8.6 ± 1.0	2.6 ± 1.1	14.7 ± 0.5	8.1 ± 0.8	79.0	0.0004	<0.005
During therapy	113.5 ± 0.8 p <0.001	6.0 ± 1.1	1.9 ± 1.1	13.7 ± 0.7	7.3 ± 1.2	68.4	0.0076	NS
BP diastolic (mm Hg)								
Pretherapy	75.2 ± 0.4	6.2 ± 0.5	2.6 ± 0.5	14.2 ± 0.3	8.5 ± 0.4	89.5*	<0.0001	<0.005
During therapy	70.2 ± 0.5 p <0.001	5.1 ± 0.8 p <0.05	1.7 ± 0.6	13.7 ± 0.6	6.9 ± 0.8	68.4	0.0018	0.001
Lisinopril								
Heart rate (beats/min)								
Pretherapy	75.1 ± 0.8	1.5 ± 1.2	1.0 ± 1.1	14.1 ± 2.9	7.7 ± 2.2	10.7	NS	NS
During therapy	72.9 ± 0.4 p <0.02	3.4 ± 0.6	1.9 ± 0.6	13.6 ± 0.6	9.9 ± 0.6	71.5*	0.0019	NS
BP systolic (mm Hg)								
Pretherapy	120.6 ± 0.6	7.1 ± 0.8	3.7 ± 0.8	14.0 ± 0.4	9.6 ± 0.4	84.1*	0.0001	<0.001
During therapy	109.1 ± 0.5 p <0.001	5.8 ± 0.7	4.1 ± 0.7	14.0 ± 0.5	8.4 ± 0.3	84.3*	<0.0001	<0.01
BP diastolic (mm Hg)								
Pretherapy	73.4 ± 0.7	6.8 ± 1.0	2.3 ± 1.0	14.4 ± 0.6	9.2 ± 0.4	71.9	0.0017	<0.001
During therapy	66.7 ± 0.6 p <0.001	3.8 ± 0.8 p <0.05	2.9 ± 0.8	13.6 ± 0.8	7.3 ± 0.5	64.2*	0.0058	NS

*Significant better fit (p at least <0.05) to a 24 hour + 12 hour rhythm than to 24 hour rhythm; 24 hour + 12 hour rhythm fit was always superior except for lisinopril heart rate pretherapy. Captopril (n = 15) was applied three times daily (8:00 a.m. and 12:00 and 5:00 p.m.) and lisinopril once daily) (8.00 A.M.). Measurements were done before and on the 5th day of treatment. Rhythm analysis was performed by cosine fit to a 24-hour and 12-hour period with PHARMFIT. Shown are mean values ± SD.

BP = blood pressure; NS = difference not significant; SD = standard deviation.

between the 2 groups. The alterations in creatinine clearance were not related to the decrease of the 24-hour means of blood pressure or to the baseline plasma renin activity.

CONCLUSION

This study shows that the circadian blood pressure rhythm is preserved in patients with mild-to-moderate heart failure. The blood pressure amplitudes are small and reduced compared to normal.[7] The degree of impairment of heart rate and blood pressure variability is dependent on the severity of left ventricular dysfunction.[7] If left ventricular function is severely impaired, circadian alterations of blood pressure may no longer be present.

Since the 24-hour blood pressure measurements are reproducible, the alterations in blood pressure during ACE inhibition represent the effect of

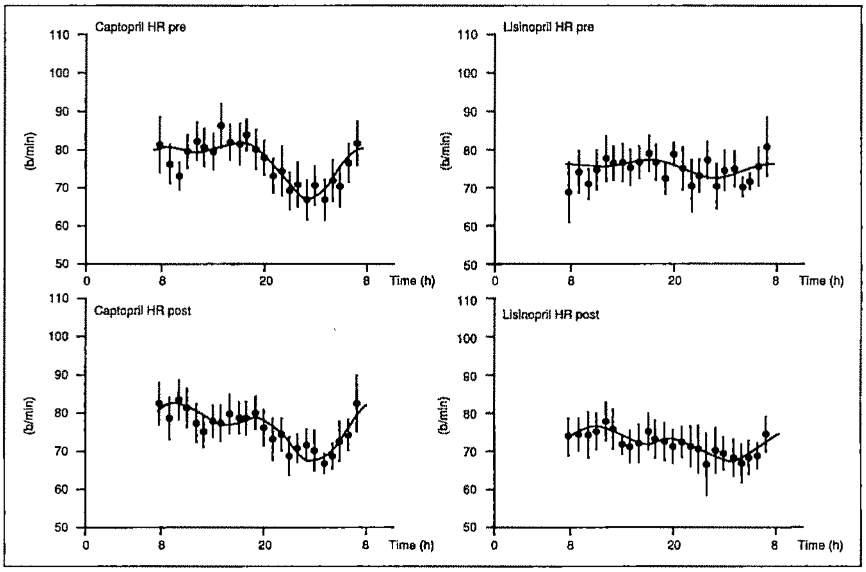

FIGURE 2. Circadian rhythm of heart rate (HR) in mild-to-moderate heart failure before (pre) and during (post, 5th day) therapy with captopril or lisinopril. Captopril was applied at 8:00 A.M., 12:00 and 5:00 P.M. and lisinopril in a single dose at 8:00 A.M. daily. Shown are mean hourly values ± standard deviation of the mean of 15 captopril and 13 lisinopril patients.

TABLE III Serum Electrolytes and Serum Creatinine and Endogenous Creatinine Clearance Before and During Therapy with Either Captopril or Lisinopril*

	Captopril		Lisinopril	
	Before Therapy	During Therapy	Before Therapy	During Therapy
Serum sodium (mmol/liter)	138 ± 1	137 ± 1	137 ± 2	134 ± 1
Serum potassium (mmol/liter)	3.8 ± 0.1†	4.3 ± 0.1‡	4.3 ± 0.1	4.3 ± 0.1
Serum creatinine (mg/dL)	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Creatinine clearance (mL/min/1.73 m^2)	63 ± 9	66 ± 10	80 ± 10	68 ± 9

*Captopril ($n = 15$) three times daily was applied (8:00 A.M. and 12:00 and 5:00 P.M.) and lisinopril ($n = 13$) in a single dose at 8:00 A.M.; measurements were done before and on the 5th day of treatment at 8:00 A.M.

†$p < 0.05$ compared to lisinopril; ‡$p < 0.01$ compared to pretreatment.

treatment and cannot be explained by a placebo effect.[8] Low doses of captopril 3 times daily and low doses of lisinopril once daily caused a significant and similar decrease in blood pressure for 24 hours in patients with mild-to-moderate heart failure. Although the low doses of ACE inhibitors used in our study are already effective, it is not clear whether increasing the dosage of ACE inhibitors would also lead to greater alterations in blood pressure.

Because of the short plasma half-life of captopril of about 1 hour and the longer effective half-life of lisinopril of 12 hours, different influences on blood pressure may be expected. Using higher doses of both ACE inhibitors in patients with severe heart failure, Packer et al[4] reported a continuously low blood pressure when enalapril was given, but intermittent increases in arterial pressure between the dosing of captopril. We did not observe such a pattern during captopril therapy, nor did we observe a continuously low arterial pressure when lisinopril was given. Two explanations are likely. First, long-term effects of captopril and lisinopril on blood pressure may depend not only on their plasma half-lives but also on a longer lasting inhibition of local vascular renin-angiotensin systems.[9] Second, periodic drug-induced alterations are so small that they will not alter the endogenous circadian blood pressure rhythm significantly in mild-to-moderate heart failure. These alterations may only be seen when blood pressure rhythm is lost, as could be expected in patients of Packer et al.[4]

A decrease in renal function is reported to occur more often during therapy with long-acting ACE inhibitors.[3,4] In a series of studies, Packer's group characterized diabetes mellitus as a risk factor for developing an increase of serum creatinine, a low mean blood pressure before ACE inhibition (<70 mm Hg), and a simultaneous activation of the renin-angiotensin system.[10] Diabetes mellitus is not likely to influence our results, because only 1 patient in each group had diabetes mellitus. Our results show that endogenous creatinine clearance was not altered significantly by either ACE inhibitor. No patient had a 24-hour mean blood pressure <70 mm Hg during ACE inhibition, and there was no correlation between the 24-hour mean blood pressure (which was used as a measure of renal perfusion pressure) during ACE inhibition and changes in creatinine clearance. It could, therefore, be assumed that blood pressure was still above the renal autoregulatory threshold in these patients. Thus, decreases in renal function are expected only in selected patients with a greater impairment of cardiac function and additional risk factors.

In conclusion, the circadian blood pressure rhythm is preserved in patients with mild-to-moderate heart failure who are living under conditions of a rest–activity cycle. Therapy with low doses of captopril 3 times daily or lisinopril once daily result in similar decreases of arterial pressure without changing the circadian blood pressure profile significantly. Renal function did not deteriorate after treatment with low doses of captopril or lisinopril.

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Pharmacokinetic Profiles of Single and Repeat Doses of Lisinopril and Enalapril in Congestive Heart Failure

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This study was undertaken to determine whether the presence of congestive heart failure (CHF) would alter absorption, first-pass metabolism, and drug elimination and result in different pharmacokinetic profiles for lisinopril and enalapril.

Lisinopril is pharmacologically active after oral administration and does not require hepatic activation. Bioavailability is low and the time to peak concentration is prolonged, mainly due to poor absorption. The drug undergoes renal elimination and has a duration effect of >24 hours.[1] Enalapril is a prodrug that requires conversion in the liver to its active form, enalaprilat. Enalaprilat is then excreted by the kidney and has a duration effect of about 24 hours.[2]

METHODS

This was an open, randomized, parallel-group study in 13 patients (≥18 years) with CHF (New York Heart Association class III–IV) on background therapy of diuretics and/or digoxin. Male and female patients were included in the study and the diagnosis of CHF was established when at least 2 of the following features were present: increased jugulovenous pressure, peripheral edema, tender hepatomegaly, or radiologic signs of pulmonary edema.

Exclusion criteria were recent myocardial infarction or stroke, aortic stenosis, primary right heart failure, systolic blood pressure <90 mm Hg, arrhythmias other than atrial fibrillation, severe liver or renal disease, malabsorption syndromes, and known sensitivity to angiotensin-converting enzyme inhibitors or indocyanine green.

Patients received either 2.5 mg lisinopril or 2.5 mg enalapril as single daily doses for 7 days. Medication was administered on day 1 and days 3–8; no drug was given on day 2 to allow for plasma concentration measurement after the first dose.

Blood samples were taken after the first dose to determine levels of serum lisinopril, enalapril, and enalaprilat predose, hourly for 12 hours and at 24, 32, and 48 hours. Hepatic blood flow was measured before the first and last dose, using indocyanine green clearance.[3] Blood pressures and heart rate were measured at baseline and 2, 4, 6, 8, 12, and 24 hours after dosing. Serum and urine concentrations of lisinopril, enalapril, enalaprilat, and angiotensin II were measured by radioimmunoassay.

Six patients received lisinopril (mean age 70 years; weight 71.8 kg) and 7 received enalapril (mean age 69 years; weight 73.7 kg). One patient

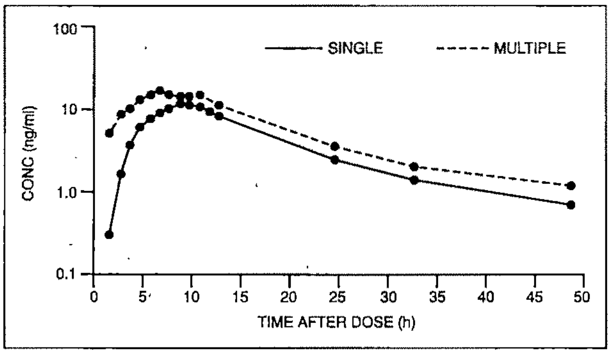

FIGURE 1. Mean serum concentrations of lisinopril (ng/mL) after single and multiple dosing in heart failure patients.

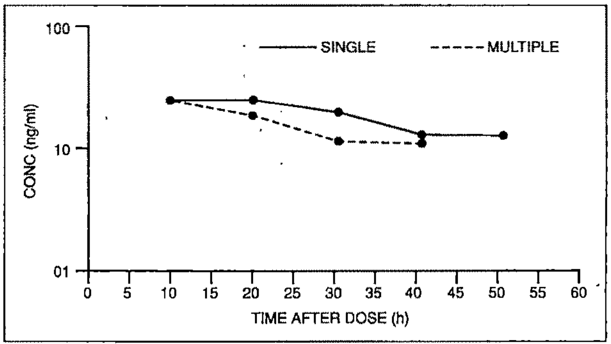

FIGURE 2. Mean serum concentrations of enalapril (ng/mL) after single and multiple dosing in heart failure patients.

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TABLE I Serum Pharmacokinetic Parameters for Lisinopril, Enalapril, and Enalaprilat in Patients with Congestive Heart Failure

	C_{max} (ng/mL)			T_{max} (hr)*		AUC (ng/mL)			
Treatment	Single Dose	Multiple Dose	Accumulation Ratio	Single Dose	Multiple Dose	Single Dose	Multiple dose	Accumulation Dose	Effective Half-Life
Lisinopril	11.5 ± 2.5	19.2 ± 2.9	1.6 ± 0.3	9	6	192.3 ± 20.6	309.4 ± 50.4	1.6 ± 0.2	16.4 ± 4.0
Enalaprilat	10.3 ± 1.8	14.8 ± 2.6	1.5 ± 0.2	8	6	218.3 ± 47.5	280.0 ± 62.7	1.3 ± 0.2	14.7 ± 3.0
Enalapril	29.0 ± 4.4	24.7 ± 4.0	—	1	1	86.9 ± 18.7	69.1 ± 21.7	—	—

*Median.
AUC = area under the plasma concentration–time curve.

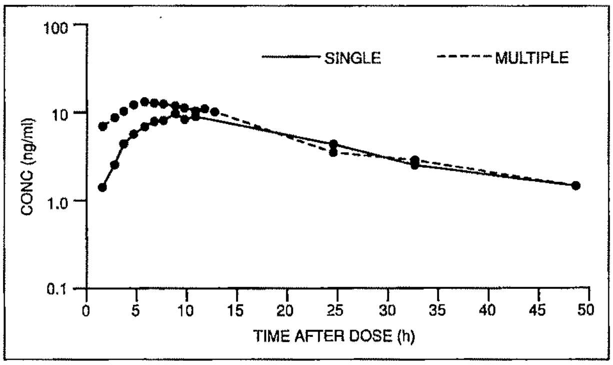

FIGURE 3. Mean serum concentrations of enalaprilat (ng/mL) after single and multiple dosing in heart failure patients.

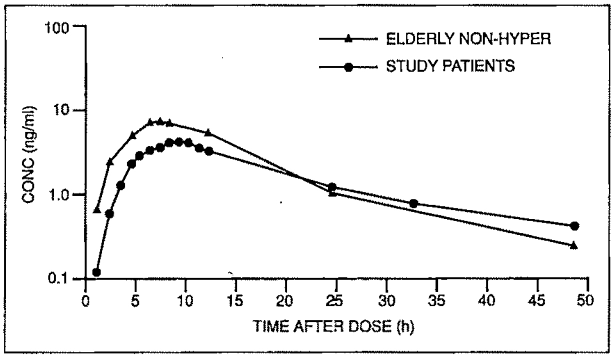

FIGURE 4. Comparison of normalized mean concentrations of lisinopril (ng/mL) after a single dose in heart failure (STUDY) patients and elderly nonhypertensive (NON-HYPER) patients.

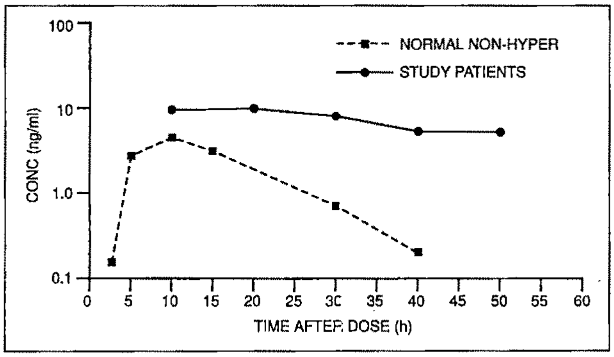

FIGURE 5. Comparison of normalized mean concentrations of enalapril (ng/mL) after a single dose in heart failure (STUDY) patients and normal nonhypertensive (NON-HYPER) patients.

TABLE II Urine Pharmacokinetic Parameters for Lisinopril, Enalapril, and Enalaprilat in Patients with Congestive Heart Failure*

	Urinary Recovery (%)		Clearance (ml/min)	
Treatment	Single Dose	Multiple Dose	Single Dose	Multiple Dose
Lisinopril	14.9 ± 3.6	29.0 ± 3.4	29.2 ± 6.5	40.6 ± 4.1
Enalaprilat	17.4 ± 2.5	28.8 ± 2.7	33.1 ± 6.7	55.0 ± 11.4
Enalapril	11.4 ± 1.5	11.8 ± 2.0	—	—

*Mean ± standard error.

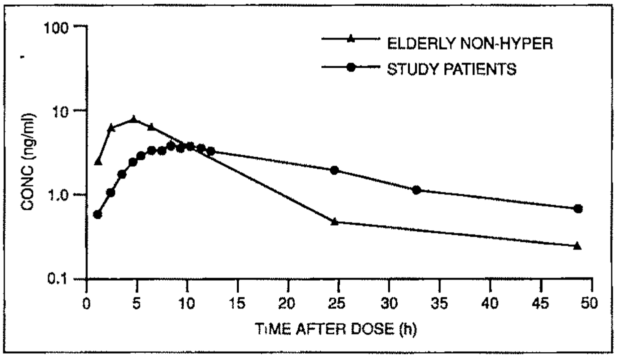

FIGURE 6. Comparison of normalized mean concentrations of enalaprilat (ng/mL) after a single dose in heart failure (STUDY) patients and elderly nonhypertensive (NON-HYPER) patients.

withdrew from lisinopril because of acute deterioration in renal function.

RESULTS

The data show that serum concentrations of lisinopril in heart failure patients were similar to those found in healthy subjects after single and multiple dosing (Table I). Mean maximum serum concentrations after 10 mg oral lisinopril in healthy subjects were about 40 ng/mL after 6–8 hours.[4–6] Assuming a linear relation between dose and peak plasma concentrations, these would represent a value of about 10 ng/mL for 2.5 mg, approximately the value seen in this study. Values calculated at 24 hours were also similar. Conversion of the prodrug enalapril to its active form, enalaprilat appeared to be delayed and reduced after single and multiple dosing. The time to, and duration of, maximum concentration of enalaprilat was increased but overall plasma concentrations were similar. CHF had minor effects on the plasma concentration–time profile of lisinopril, enalapril and its active metabolite enalaprilat after single and multiple dosing (Figures 1–6). Decreases in gastrointestinal absorption and first-pass metabolism were compensated for by reduced renal clearance (Table II). Neither drug altered hepatic blood flow after either acute or chronic administration.

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Cardiology (UCM)

OCTOBER 15, 1992

971 **Coronary Artery Disease**
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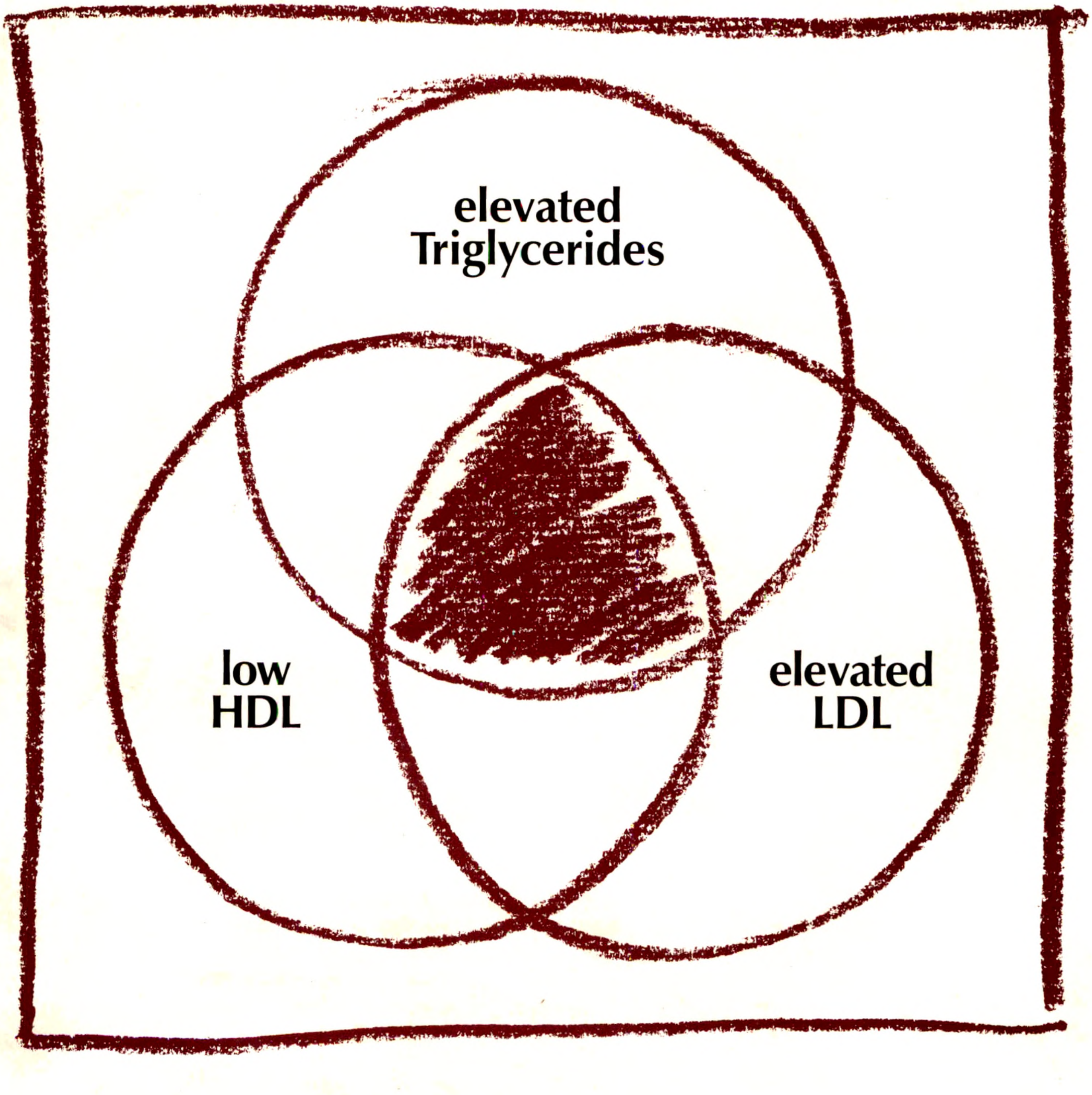

ergonovine and ISDN in some segments. These observations indicate that low-dose administration of intracoronary ergonovine produces sufficient coronary artery vasoconstriction, similar to or slightly greater than that of intraaortic ergonovine, but basal coronary tone may influence the vasoreactivity to ergonovine.

PREVENTIVE CARDIOLOGY

1010

Treatment of Refractory Familial Hypercholesterolemia by Low-Density Lipoprotein Apheresis Using an Automated Dextran Sulfate Cellulose Adsorption System

Bruce R. Gordon, Sheryl F. Kelsey, David W. Bilheimer, David C. Brown, Peter C. Dau, Antonio M. Gotto, Jr., D. Roger Illingworth, Peter H. Jones, Susan F. Leitman, James Prihoda, Evan A. Stein, Thomas N. Stern, James H. Zavoral, and Robert J. Zwiener, for the Liposorber Study Group

Lipid and lipoprotein changes using the Liposorber® LA-15 System were evaluated in a 9-center, controlled study of patients with familial hypercholesterolemia (FH) who had not responded adequately to diet and drug therapy. There were 54 patients with heterozygous FH (45 randomized to treatment, and 9 control subjects) and 10 with homozygous FH (all of whom received LDL apheresis). The system uses dextran sulfate cellulose as the adsorbent to selectively remove apolipoprotein B–containing particles from plasma. Mean acute reductions in LDL cholesterol were 76% in heterozygous FH patients and 81% in homozygous ones. Time-averaged levels of LDL cholesterol were reduced 41% in heterozygous FH patients and 53% in homozygous ones. The substantial acute reduction of lipoprotein (a) (means: 65%, heterozygous FH; 68%, homozygous FH) has not been reported with other therapies. The Liposorber LA-15 system represents an important therapeutic option in FH patients who respond inadequately to diet and drug therapy.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1017

Measurement of Ventricular Electrogram Amplitude During Intraoperative Induction of Ventricular Tachyarrhythmias

Kenneth A. Ellenbogen, Mark A. Wood, Bruce S. Stambler, William J. Welch, and Ralph J. Damiano

Adequate sensing of ventricular tachycardia and ventricular fibrillation (VF) is necessary for proper functioning of an implantable cardioverter defibrillator (ICD). Mean amplitude of intracardiac electrograms (ICEGM) recorded with bipolar epicardial or transvenous sensing leads was measured in 63 patients during induced ventricular tachyarrhythmias at the time of implantable cardioverter defibrillator implantation. Mean amplitude of the ICEGM during 41 episodes of VF in 15 patients decreased from 14.9 ± 0.9 mV during sinus rhythm to 8.8 ± 0.7 mV at 1 second, 9.7 ± 0.7 mV at 5 seconds, and 9.4 ± 0.7 mV at 10 seconds (p

<0.0001 vs sinus rhythm ICEGM) with endocardial leads. Mean amplitude of the ICEGM recorded during 173 episodes of VF in 43 patients with epicardial leads decreased from 10.4 ± 0.3 mV in sinus rhythm to 7.8 ± 0.3 mV at 1 second, 8.3 ± 0.3 mV at 5 seconds and 8.0 ± 0.3 mV at 10 seconds (p <0.0001 vs sinus rhythm ICEGM). Despite the absence of significant changes in mean ICEGM amplitude during time in VF, about 60% of episodes were associated with a twofold or greater change in ICEGM amplitude during VF at each time measured. It is concluded that fixed gain devices must have sufficiently low programmable sensitivities to compensate for changes in ICEGM amplitude with time.

1023

Effects of Chronic Amiodarone Therapy on Defibrillation Threshold

Werner Jung, Matthias Manz, Luciano Pizzulli, Dietrich Pfeiffer, and Berndt Lüderitz

In a prospective and parallel randomized study, the long-term stability of epicardial defibrillation thresholds was evaluated in 22 patients, using a patch-patch lead configuration at the time of implantation and generator replacement. The concomitant antiarryhthmic drug therapy consisted of either mexiletine (720 mg/day) or amiodarone (400 mg/day) and was administered to patients in a parallel, randomized manner. During a mean follow-up of 24 ± 6 months, the defibrillation threshold increased significantly from 14.3 ± 2.8 to 17.9 ± 5.3 J (p <0.05) for the entire patient group. The increase in the chronic defibrillation threshold was due to a marked increase in defibrillation energy needs in the subgroup of patients receiving amiodarone. Whereas no significant change in the defibrillation threshold was documented in the subgroup of patients receiving mexiletine, the mean defibrillation threshold increased from 14.1 ± 3.0 to 20.9 ± 5.4 J (p <0.001) in those receiving amiodarone.

1028

Beta-Blocking Effect of Propafenone Based on Spectral Analysis of Heart Rate Variability

Federico Lombardi, Daniela Torzillo, Giulia Sandrone, Laura Dalla Vecchia, Maria Luisa Finocchiaro, Roberto Bernasconi, and Emanuele Cappiello

Spectral analysis of RR variability was used to evaluate whether the antiarrhythmic effects of propafenone (a 1C drug structurally related to β blockers) are associated with alterations in neural control mechanisms. The drug determined a relevant reduction in overall RR variability. Furthermore, it caused a significant decrease in the low-frequency component (a marker of sympathetic activation) and a marked increase in the high frequency component (a marker of parasympathetic modulation) of RR variability. These changes were consistent with a shift in sympathovagal balance toward a parasympathetic predominance and a reduced sympathetic tone. Propafenone administration was also associated with a significant attenuation of the increase in the low-frequency component induced by tilt. These results indicate that propafenone has antiadrenergic proper-

Continued on page A28

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SYSTEMIC HYPERTENSION

1035

Stress Response Pattern in Obesity and Systemic Hypertension

Jürgen K. Rockstroh, Roland E. Schmieder, Hartmut Schächinger, and Franz H. Messerli

The hemodynamic response to mental stress and to isometric exercise in lean and obese hypertensive patients was determined. During mental stress, obese subjects responded with a higher increase in total peripheral resistance and diminished increases in heart rate, cardiac output and stroke volume than their lean counterparts. During isometric stress, an exaggerated increase in systolic and diastolic pressures, and heart rate were observed in the obese hypertensive group compared with measurements in lean patients. Body mass index emerged as an independent determinant of the increase in systolic and diastolic pressures as well as of total peripheral resistance. These results indicate that obese hypertensive patients respond to (1) mental stress with exaggerated vasoconstriction and to (2) isometric stress with an exaggerated increase in arterial pressure, thereby arguing against the concept that obesity would be prone to mitigate the effects of hypertensive vascular disease.

VALVULAR HEART DISEASE

1040

Transesophageal Echocardiographic Monitoring of Percutaneous Mitral Balloon Valvulotomy

Isidre Vilacosta, Elena Iturralde, José Alberto San Román, Manuel Gómez Recio, Claudio Romero, Javier Jiménez, and Luis Martínez-Elbal

This study was designed to evaluate the usefulness of transesophageal echocardiography (TEE) during percutaneous mitral balloon valvulotomy (PMBV). Two groups of patients were studied who underwent PMBV (one aided by TEE and the other not). TEE was most helpful in guiding transseptal puncture, assessing the proper position of the balloon and enabling early detection of complications. Furthermore, there was a tendency to decrease the frequency of significant mitral regurgitation. TEE decreased the x-ray exposure time and was well-tolerated. Thus, TEE provides useful information that makes PMBV safer and easier to perform.

1045

Quantitative Dynamics of Left Ventricular Emptying and Filling as a Function of Heart Size and Stroke Volume in Pure Aortic Regurgitation and in Normal Subjects

John A. Rumberger and Judd E. Reed

The absolute and relative peak rates of systolic emptying and early diastolic filling were determined using cine computed tomography in 15 normal male patients and 15 male patients with compensated volume overload

Continued on page A31

from isolated aortic insufficiency. All patients had normal ejection fraction and were of similar ages and heart rates. Absolute peak left ventricular emptying and filling rates were greater in the patients with volume overload but the values varied linearly with both end-diastolic and stroke volumes. However, the ratio of peak emptying to peak filling rate was constant in all subjects. Referencing rates of emptying and filling to ventriciular size (end-diastolic volume) or stroke volume, or both, eliminated the intersubject differences. In conclusion, in patients with normal ejection fractions, the left ventricle compensates for increases in ventricular size or forward stroke volume, or both, by increasing the rate of emptying and filling proportionately.

MISCELLANEOUS

1051

Effects on Platelet Aggregation and Fibrinolytic Activity During Upright Posture and Exercise in Healthy Men

Kaj Winther, William Hillegass, Geoffrey H. Tofler, Alfredo Jimenez, Damian A. Brezinski, Andrew I. Schafer, Joseph Loscalzo, Gordon H. Williams, and James E. Muller

The circadian variation of acute myocardial infarction suggests that daily activities may trigger the onset of coronary thrombosis. Such triggering may result from unfavorable alterations in the balance between the prothrombotic and antithrombotic properties of the blood. The present study compares the effects of 2 common daily activities assuming the upright posture and exercise — on platelet aggregation and fibrinolytic activity. In healthy male subjects, taking the upright posture in the morning significantly increased platelet aggregation and produced only a moderate increase in fibrinolytic activity within 10 minutes. These changes recurred when upright posture was assumed later in the day. Exercise did not increase platelet aggregation to levels beyond that produced by the upright posture, but was associated with a marked increase in fibrinolytic activity. Thus, exercise and assumption of the upright posture produce distinctive alterations in the thrombogenic potential of the blood that may influence the timing of clinical vascular events.

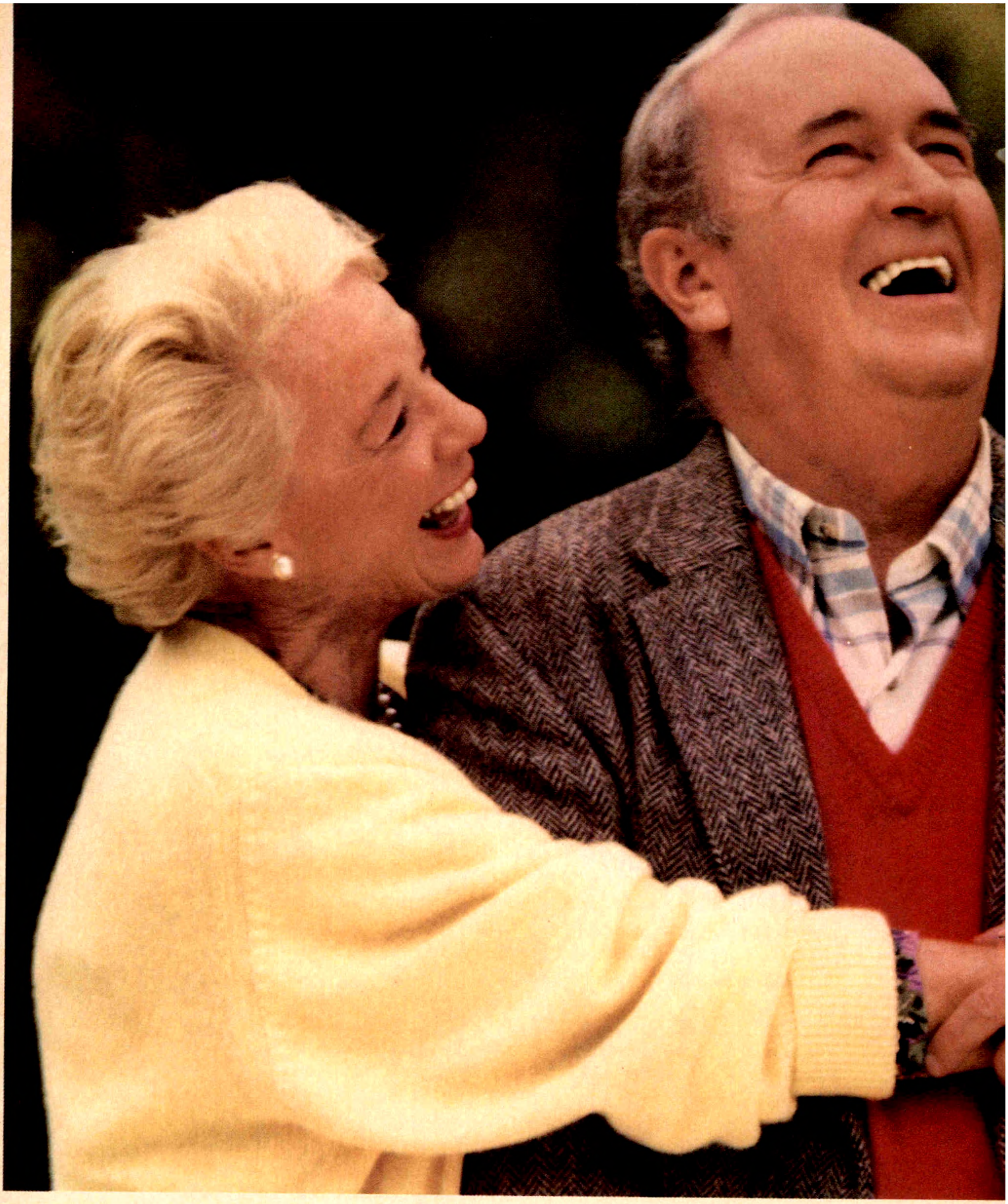
1056

Transesophageal Echocardiography to Assess Mitral Valve Function and Flow During Cardiopulmonary Resuscitation

Thomas R. Porter, Joseph P. Ornato, Cathy S. Guard, Valerie G. Roy, Carolyn A. Burns, and J. V. Nixon

Transesophageal Doppler echocardiography was performed during cardiopulmonary resuscitation in 17 patients using a mechanical piston compression device to assess mitral valve position and flow during chest compression, and their relation to left ventricular fractional shortening. Patients were divided into 2 groups on the basis of whether the mitral valve closed with chest compression (group I; n = 12) or remained open or opened further (group II; n = 5). Although left ventricular dimensions and fractional shortening did not differ between groups, peak transmitral flow and time-velocity integrals were significantly higher in group I.

Continued on page A35



*In hypertension, CAPOTEN may be used as initial therapy (25 mg bid or tid) for patients with normal renal function, in whom the risk of neutropenia/agranulocytosis is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

†In heart failure, CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy**, on the adjacent page.

Furthermore, peak transmitral flow occurred during the release phase in group I, whereas it occurred during compression in group II. These findings demonstrate that although mitral valve closure occurs in most patients with chest compression during cardiopulmonary resuscitation, the mechanism for closure appears independent of direct left ventricular compression.

1061

Arrhythmias After Cardiac Transplantation

Christopher D. Scott, John H. Dark, and Janet M. McComb

Fifty adult heart transplant recipients surviving >2 weeks were studied by continuous hospital telemetry and ambulatory electrocardiographic monitoring at 2, 4, 6, 12 and 24 weeks after operation. Atrial premature complexes were significantly more frequent among rejectors than nonrejectors in the early postoperative period. Atrial flutter was the most frequent sustained arrhythmia; it was closely associated with rejection, and its occurrence should be regarded as an indication for endomyocardial biopsy. Ventricular premature complexes were universal in the early period after transplantation, and their frequency was unrelated to rejection, but decreased significantly with time after transplantation. Ventricular tachycardia was recorded once and was probably a proarrhythmic effect of flecainide.

METHODS

1064

A New Technique for Simultaneous Monitoring of Electrocardiogram and Walking Cadence

Jeffrey M. Hausdorff, Daniel E. Forman, David M. Pilgrim, David R. Rigney, and Jeanne Y. Wei

A new technique for simultaneously recording continuous electrocardiographic (ECG) data and walking step rate (cadence) is described. The output of force-sensitive foot switches is frequency-modulated and recorded on 1 channel of an ambulatory Holter monitor, whereas the electrocardiogram is recorded on the other. The footfall signal provides an indication of the subject's activity (walking or standing), as well as the instantaneous walking rate. Initial investigation revealed the following: (1) There was an inverse relation between heart rate (HR) and cadence variability ($r = -0.73$). Three elderly subjects with no known cardiac disease had HR and cadence variability similar to those of the young, whereas elderly subjects with history of congestive heart failure were among those with the lowest HR variability and the highest cadence variability. (2) Low-frequency ($\cong 0.1$ Hz) HR oscillations persisted during walking in all young subjects. (3) In some subjects, both step rate and HR oscillated at the same low frequency ($\cong 0.1$ Hz) previously identified with autonomic control of the

Continued on page A38

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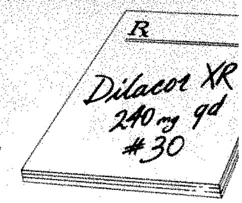

BRIEF SUMMARY

CONTRAINDICATIONS

Diltiazem hydrochloride is contraindicated in: (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker; (2) patients with second or third degree AV block except in the presence of a functioning ventricular pacemaker; (3) patients with hypotension (less than 90 mmHg systolic); (4) patients who have demonstrated hypersensitivity to the drug; and (5) patients with acute myocardial infarction and pulmonary congestion as documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. Diltiazem hydrochloride prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second, or third degree AV block (22 of 10,119 patients, or 0.2%); 41% of these 22 patients were receiving concomitant ß-adrenoceptor antagonists versus 17% of the total group. Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single 60 mg dose of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction of 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of diltiazem hydrochloride in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with diltiazem hydrochloride therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of serum transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 6 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some others (see PRECAUTIONS).

PRECAUTIONS

General. Diltiazem hydrochloride is extensively metabolized by the liver and is excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with the histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS) may be transient and may disappear despite continued use of diltiazem hydrochloride. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Although Dilacor™ XR utilizes a slowly disintegrating matrix, caution should still be used in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been no reports of obstructive symptoms in patients with known strictures in association with the ingestion of Dilacor™ XR.

Information for Patients. Dilacor™ XR capsules should be taken on an empty stomach. Patients should be cautioned that the Dilacor™ XR capsules should not be opened, chewed or crushed, and should be swallowed whole.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem hydrochloride concomitantly with any agents known to affect cardiac contractility and/or conduction (see WARNINGS). Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem hydrochloride (see WARNINGS). As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem hydrochloride undergoes biotransformation by cytochrome P-450 mixed function oxidase. Co-administration of diltiazem hydrochloride with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered diltiazem hydrochloride to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem hydrochloride and beta-blockers is usually well-tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities. Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and the bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem hydrochloride with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem hydrochloride therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium channel blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in ra
study in mice showed no evidence of carcinogenicity. There was also no mutage
or *in vivo* in mammalian cell assays or *in vitro* in bacteria. No evidence of ir
observed in male or female rats at oral doses of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice
Administration of doses ranging from 4 to 6 times (depending on species) the up
mum dosage range in clinical trials (480 mg q.d. or 8 mg/kg q.d. for a 60 kg pat
embryo and fetal lethality. These studies have revealed, in one species or anot
cause abnormalities of the skeleton, heart, retina, and tongue. Also observed
early individual pup weights and pup survival, prolonged delivery and increas
births.

There are no well-controlled studies in pregnant women; therefore, use diltiaz
pregnant women only if the potential benefit justifies the potential risk to the fetu

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests th
breast milk may approximate serum levels. If use of diltiazem hydrochloride is d
alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions to diltiazem hydrochloride have been rare in studies
tions, as well as with Dilacor™ XR. It should be recognized, however, that pa
ventricular function and cardiac conduction abnormalities have usually been e
studies.

The most common adverse events (frequency ≥1%) in placebo-controlled, clinica
ies with Dilacor™ XR using daily doses up to 540 mg are listed in the table t
treated patients included for comparison.

MOST COMMON ADVERSE EVENTS
IN DOUBLE-BLIND, PLACEBO-CONTROLLED HYPERTENSION TRI

Adverse Events (COSTART Term)	Dilacor™ XR n=303 # pts (%)	
rhinitis	29 (9.6)	
headache	27 (8.9)	1
pharyngitis	17 (5.6)	
constipation	11 (3.6)	
cough increase	9 (3.0)	
flu syndrome	7 (2.3)	
edema, peripheral	7 (2.3)	
myalgia	7 (2.3)	
diarrhea	6 (2.0)	
vomiting	6 (2.0)	
sinusitis	6 (2.0)	
asthenia	5 (1.7)	
pain, back	5 (1.7)	
nausea	5 (1.7)	
dyspepsia	4 (1.3)	
vasodilatation	4 (1.3)	
injury, accident	4 (1.3)	
pain, abdominal	3 (1.0)	
arthrosis	3 (1.0)	
insomnia	3 (1.0)	
dyspnea	3 (1.0)	
rash	3 (1.0)	
tinnitus	3 (1.0)	

*Adverse events occurring in 1% or more of patients receiving Dilacor™ XR.

The following additional events (COSTART Terms), listed by body system, w
quently in all subjects and hypertensive patients who received Dilacor™ XR (n=4
First-degree AV block, arrhythmia, postural hypotension, tachycardia, pallor, pa
ECG abnormality, ST elevation; Nervous System: Vertigo, hypertonia, paresthesi
lence; Digestive System: Dry mouth, anorexia, tooth disorder, eructation; Ski
Sweating, urticaria, skin hypertrophy (nevus); Respiratory System: Epistaxis, br
disorder; Urogenital System: Cystitis, kidney calculus, impotence, dysmenorrhe
disease; Metabolic and Nutritional Disorders: Gout, edema; Musculoskeletal Syst
sitis, bone pain; Hemic and Lymphatic Systems: Lymphadenopathy; Body as a W
able reaction, neck pain, neck rigidity, fever, chest pain, malaise; Special Senses:
vision), ear pain.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem hydrochloride has been limited. Th
ipecac to induce vomiting and activated charcoal to reduce drug absorption have
initial means of intervention. In addition to gastric lavage, the following meas
considered:

Bradycardia: Administer atropine (0.60 to 1.0 mg). If there is no response to vagal
ter isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high-degree AV bloc
with cardiac pacing.

Cardiac Failure: Administer inotropic agents (dopamine or dobutamine) and diure

Hypotension: Vasopressors (*e.g.* dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situa
judgment and experience of the treating physician.

Due to extensive metabolism, plasma concentrations after a standard dose of dilti
tenfold, which significantly limits their value in evaluating cases of overdosage.

Charcoal hemoperfusion has been used successfully as an adjunct therapy to h
tion. Overdoses with as much as 10.8 gm of oral diltiazem have been succes
appropriate supportive care.

CAUTION: FEDERAL (U.S.A.) LAW PROHIBITS DISPENSING WITHOUT PRESCRIP

Please see product circular for full prescribing information.

References:

1. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc.
2. *1992 Drug Topics® Red Book® Update.* Oradell, NJ, Medical Economics Co. Inc.; April, 1992.

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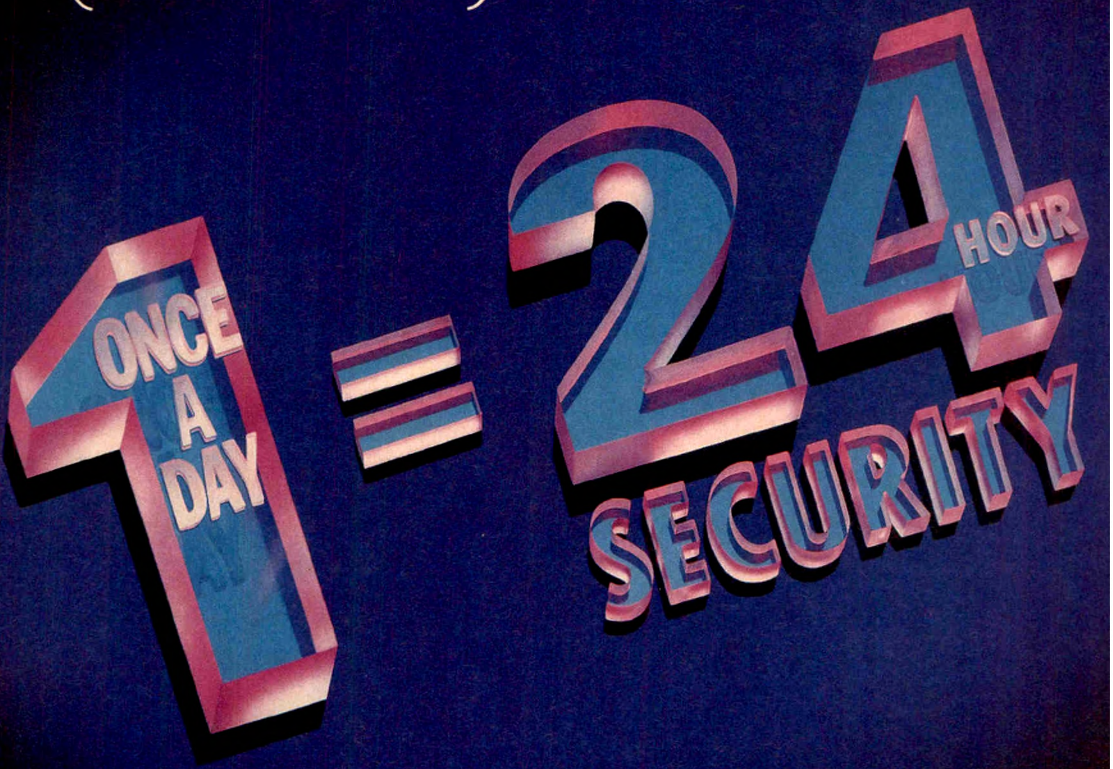

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DILACOR XR offers the classic diltiazem safety profile across the entire dosing range[1]

DILACOR XR makes diltiazem a cost-effective choice for the treatment of hypertension[2]

CARDIOVASCULAR PHARMACOLOGY

1072

Impact of Food on the Pharmacokinetics and Electrocardiographic Effects of Sustained Release Verapamil in Normal Subjects

Timothy J. Hoon, Patrick L. McCollam, Karen J. Beckman, Robert J. Hariman, and Jerry L. Bauman

To evaluate the impact of food on the pharmacokinetics and electrocardiographic effects of sustained release (SR) verapamil, 9 healthy men each received 10 mg of intravenous verapamil, 240 mg SR verapamil on an empty stomach, and 240 mg SR verapamil with a standardized meal. The time to peak concentration was longer (7.5 ± 3.0 vs 4.4 ± 2.3 hours), resulting in a lower peak verapamil serum concentration (118 ± 43 vs 175 ± 50 ng/ml) when SR verapamil was administered with food ($p < 0.05$). Precipitous or exaggerated release of verapamil from the SR tablet was not observed in any subject during the fasting state. Prolongation of the PR interval paralleled these alterations in serum concentration. The maximal percent change in the PR interval was greater (21 ± 8 vs 14 ± 5%; $p < 0.05$) when SR verapamil was given in the fasting state. Although an exaggerated verapamil release or effect was not observed, food significantly altered the absorption and electrocardiographic effects of SR verapamil. Manipulation of the administration condition may be helpful in achieving desired outcomes.

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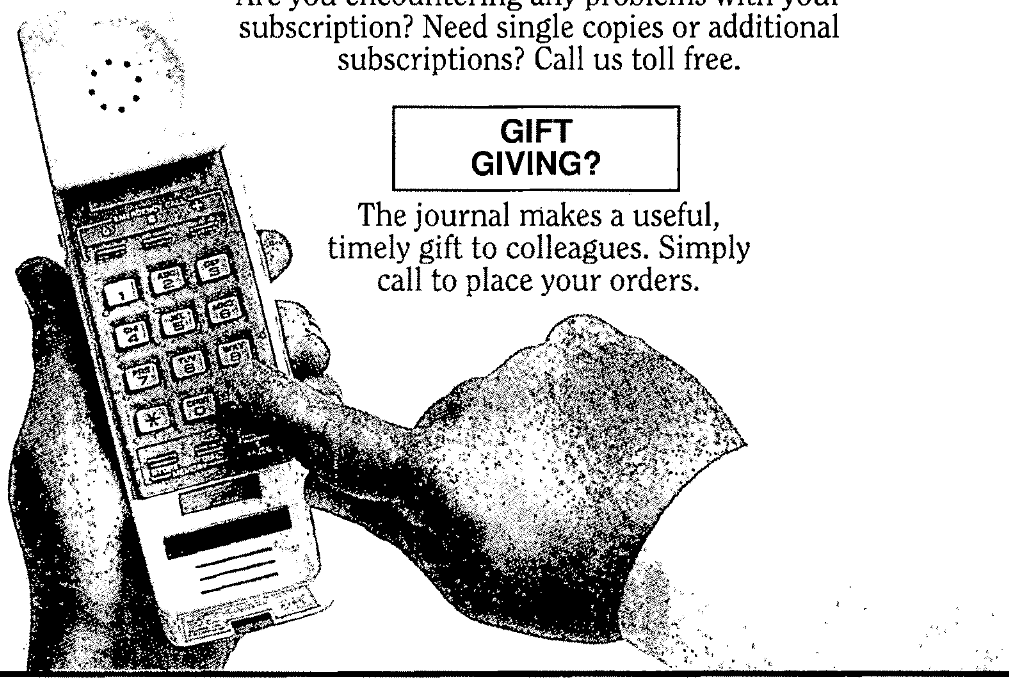

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CORONARY ARTERY DISEASE

American Journal of Cardiology

OCTOBER 15, 1992, VOL. 70, NO. 11

Echocardiographic Determinants of Clinical Outcome in Subjects with Coronary Artery Disease (the Framingham Heart Study)

Maurizio Galderisi, MD, Michael S. Lauer, MD, and Daniel Levy, MD

Echocardiographic predictors of clinical outcome were examined in subjects from the Framingham Heart Study with overt coronary artery disease. The study population consisted of 185 men and 147 women with coronary artery disease who underwent M-mode echocardiography and were followed for a mean of 3.90 years. At baseline, 37 men (18.4%) and 16 women (10.9%) had reduced fractional shortening, 43 men (23.2%) and 28 women (19%) had left ventricular (LV) dilatation, and 76 men (41%) and 76 women (51.7%) had LV hypertrophy. During the follow-up period new cardiovascular disease events (coronary disease, stroke, transient ischemic attack, claudication, heart failure and deaths from cardiovascular disease) occurred in 60 men (32%) and 58 women (39%). With use of age-adjusted proportional hazards analyses, LV mass/height in men (relative risk [RR] = 1.25/50 g/m increment, 95% confidence interval [CI] 1.01 to 1.55) and LV end-diastolic diameter in women (RR = 1.36/5 mm increment, 95% CI 1.05 to 1.76) were predictors of new cardiovascular disease events. Cardiovascular risk was also associated with LV end-systolic diameter in both sexes (in men RR = 1.28/1 SD increment, 95% CI 1.02 to 1.63; in women RR = 1.40/1 standard deviation increment, 95% CI 1.09 to 1.82). Reduced fractional shortening alone (RR = 1.91, 95% CI 1.11 to 3.31) and in combination with LV dilatation (RR = 2.13, 95% CI 1.13 to 4.02) was associated with the incidence of new cardiovascular disease outcomes in men. In women, cardiovascular risk was increased with LV hypertrophy (RR = 2.30, 95% CI 1.29 to 4.12), high LV wall thickness (RR = 3.36, 95% CI = 1.18 to 9.55), high LV end-systolic diameter (RR = 2.59, 95% CI 1.45 to 4.62) and a combination of low fractional shortening and LV dilatation (RR = 3.25, 95% CI 1.28 to 8.25). Thus, M-mode echocardiography has prognostic value in identifying subjects with coronary artery disease who are at increased risk for new morbid or fatal events.

(Am J Cardiol 1992;70:971-976)

M-mode echocardiography is a widely used technique that provides accurate noninvasive measurement of cardiac structure and function. Because of ease of performance, it has assumed a prominent role in clinical trials and epidemiologic studies.[1] Echocardiographically determined left ventricular (LV) hypertrophy has been identified as a strong, independent predictor of cardiovascular morbidity and mortality in subjects free of overt coronary artery disease.[2-5] LV function is a key determinant of prognosis in patients with coronary artery disease[6,7] and is the major predictor of mortality after myocardial infarction.[8,9] There is relatively little known about echocardiographic features of subjects with overt coronary artery disease who are at high risk for morbid or fatal sequelae.[10] The present study was undertaken to examine the M-mode echocardiographic predictors of new clinical cardiovascular disease events in Framingham Heart Study subjects with overt coronary artery disease.

METHODS

Study population: The Framingham Heart Study began in 1948 when a sample of the population of Framingham, Massachusetts, between the ages of 30 and 62 years, was enrolled in a prospective epidemiologic study. Offspring of the original cohort (and spouses of these offspring) were entered into a prospective offspring study in 1971. The selection criteria and study design have been described previously.[11,12] From 1979 to 1983, M-mode echocardiograms were performed on the surviving original cohort subjects undergoing their sixteenth biennial examination and in the offspring study subjects undergoing their second examination. These examinations also included 12-lead electrocardiograms, anthropometric measurements and determina-

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tion of blood glucose levels. Diabetes mellitus was defined by any 1 of the following: a fasting whole blood glucose level ≥7.77 mmol/liter (140 mg/dl), a random nonfasting whole blood glucose level ≥11.11 mmol/liter (200 mg/dl), or the use of insulin or an oral hypoglycemic agent. Data regarding cigarette smoking and measurements of plasma total cholesterol and high-density lipoprotein cholesterol were obtained at the fifteenth biennial examination of the original cohort and the second examination of offspring study subjects.

To be eligible for inclusion in this study subjects had to have adequate quality echocardiograms and clinical evidence of coronary artery disease. Overt coronary artery disease was identified through medical history, physical examination and hospital records and included angina pectoris, coronary insufficiency and myocardial infarction. Criteria for the various coronary artery disease outcomes have been published previously.[13] Echocardiograms were not used to determine the presence or absence of coronary artery disease.

Outcome events: New cardiovascular disease events were identified at each examination (every 2 years for original cohort and every 4 years for offspring study cohort) by medical history, physical examination, 12 lead-electrocardiogram and review of hospital records. Medical records were routinely obtained for subjects who did not appear for an examination and were evaluated for evidence of incident cardiovascular disease. All suspected cardiovascular events were reviewed by 3 physicians who evaluated the pertinent records. Cardiovascular disease events included myocardial infarction and sudden or non-sudden death attributed to coronary artery disease, congestive heart failure, stroke or transient ischemic attack, intermittent claudication and deaths due to cardiovascular disease.

All deaths were evaluated similarly, and the likely cause was established on the basis of the hospital records, autopsy findings, death certificates, and interviews with family members. Deaths from cardiovascular disease included deaths due to coronary artery disease, stroke and other cardiovascular causes.

Echocardiographic methods: The echocardiographic methods used in the Framingham Heart Study have been described previously.[14] Subjects were studied using a standard M-mode echocardiographic technique. Measurements of the left ventricle were performed at end-diastole according to both American Society of Echocardiography recommendations[15] and the "Penn" convention.[16] LV mass was determined by the following equation used in conjunction with Penn convention measurements: LV mass (in grams) = $1.04\ [(\text{LVIDD} + \text{VST} + \text{PWT})^3 - (\text{LVIDD})^3] - 13.6$, where LVIDD = LV internal diameter in diastole, VST = ventricular septal thickness, and PWT = posterior wall thickness. LV mass (in grams) was normalized for height (in meters) as previously reported.[14] The sum of LV wall thickness was defined as the sum of the ventricular septum and posterior wall thickness at end-diastole. Relative wall thickness was calculated as the ratio of ventricular septal thickness + posterior wall thickness divided by LV diastolic diameter. Fractional shortening was computed as the ratio of LV diastolic diameter–LV end-systolic internal diameter divided by LV diastolic diameter.

Sex-specific echocardiographic criteria derived from a healthy reference population from Framingham were used to define normal and abnormal population-based values for various echocardiographic parameters. The reference population consisted of 608 men and 1,134 women without evidence of overt cardiovascular disease, diabetes mellitus, hypertension (defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), pulmonary disease, and taking no cardiovascular medications, and with a body mass index ranging between 19 and 26 kg/m^2 (corresponding to Metropolitan relative weights between 90 and 120%, respectively).

Mean values and standard deviations for the echocardiographic parameters in the healthy reference population were determined. LV mass/height was 100.3 ± 22.9 g/m in men and 71.9 ± 14.7 g/m in women, the sum of LV wall thickness was 18.5 ± 2.3 mm in men and 16.0 ± 1.8 mm in women, and relative wall thickness was 0.36 ± 0.05 in men and 0.35 ± 0.05 in women. Diastolic LV diameter was 50.5 ± 3.8 mm in men and 45.5 ± 3.2 mm in women, end systolic LV internal diameter was 32.5 ± 3.4 mm in men and 28.3 ± 3.7 mm in women, and fractional shortening was 0.36 ± 0.04 in men and 0.38 ± 0.04 in women. LV hypertrophy was defined as LV mass/height equal or higher than the 95th percentile of the healthy reference population. Values for increased LV wall thickness, LV dilatation (= high LV diastolic diameter), and high end-systolic LV internal diameter were established in the same manner. Low fractional shortening was defined as a value equal or less than the fifth percentile of the reference population. Cut-points for the dichotomous echocardiographic parameters were: LV hypertrophy–LV mass/height, ≥141 g/m in men and ≥98 g/m in women; increased LV wall thickness–sum of wall thickness, ≥22 mm in men and 18 mm in women; high relative wall thickness, ≥0.46 in men and ≥0.44 in women; LV dilatation–LV diastolic diameter, ≥56 mm in men and ≥51 mm in women; high LV systolic diameter, ≥38 mm in men and ≥33 mm in women; and low fractional shortening, ≤0.30 in men and ≤0.32 in women.

Statistical methods: The mean follow-up period for the participants was 3.90 years. Sex-specific analyses were performed. The outcome events studied were nonfatal or fatal cardiovascular disease events. The incidence of these outcomes was examined both as a function of continuous echocardiographic parameters (e.g., LV mass/height) and as a function of the presence or absence of dichotomous echocardiographic abnormalities (e.g., LV hypertrophy). In addition, combinations of dichotomous echocardiographic abnormalities that represent concomitant alterations in LV function and structure (e.g., low fractional shortening with LV dilatation) were studied. Age-adjusted rates of cardiovascular disease events were calculated by the direct method. The Cox proportional hazards model[17] was used to examine the relations between echocardiographic variables and the incidence of cardiovascular disease events. All analyses were age-adjusted. Age-adjusted relative

TABLE I Characteristics of the Study Subjects

Characteristics	Men (n = 185)	Women (n = 147)
Age (years)	63.2 ± 10.5	68.3 ± 9.8
Systolic blood pressure (mm Hg)	134.4 ± 17.8	141.3 ± 23.7
Diastolic blood pressure (mm Hg)	78.8 ± 9.4	75.4 ± 12.3
Body mass index (kg/m^2)	27.0 ± 3.4	27.0 ± 4.9
Total:HDL cholesterol	5.9 ± 1.8	5.5 ± 1.8
Cigarette smokers (%)	28.7	23.8
Diabetes mellitus (%)	12.0	17.0
LV mass/height (g/m)	140.6 ± 49.9	111.3 ± 42.6
Septal wall thickness (mm)	21.4 ± 3.9	20.1 ± 4.0
Relative wall thickness	0.41 ± 0.09	0.44 ± 0.11
LV diastolic diameter (mm)	52.6 ± 6.3	46.2 ± 5.5
LV systolic diameter (mm)	34.7 ± 5.8	28.6 ± 5.2
Fractional shortening	0.34 ± 0.07	0.38 ± 0.05

Values are mean ± SD.
HDL = high-density lipoprotein; LV = left ventricular.

TABLE II Prevalence of Abnormal Echocardiographic Parameters

	Men No. (%)	Women No. (%)
LV hypertrophy	76 (41.0)	76 (51.7)
High LV wall thickness	80 (43.2)	118 (80.3)
High relative wall thickness	39 (21.1)	53 (36.0)
LV dilatation	43 (23.2)	28 (19.0)
High LV systolic diameter	46 (24.9)	26 (17.7)
Low fractional shortening	37 (18.4)	16 (10.9)
Low fractional shortening + LV dilation	23 (12.4)	8 (5.4)
Low fractional shortening + LV hypertrophy	21 (11.4)	13 (8.8)

LV = left ventricular.

sk (RR) values (and 95% confidence intervals [CI]) r outcome events were calculated for increments of hocardiographic continuous variables (corresponding 1 standard deviation within the study population) and r the presence or absence of dichotomous variables on e basis of the coefficients derived from the age-adjust- d proportional hazards models.

To examine the cumulative impact of echocardio- raphic abnormalities, age-adjusted event rates (per ,000 patient-years) were examined as a function of the resence of (1) LV hypertrophy, (2) reduced fractional ortening, or (3) increased end-systolic LV diameter. ge-adjusted rates were calculated based on the pres- nce of 0, 1, and 2 or more abnormalities.

ESULTS

Study population: The characteristics of the study opulation are listed in Table I. Of the 2,805 men and ,413 women who attended the index examination, 185 en and 147 women had evidence of overt coronary rtery disease and adequate quality echocardiograms. he study population included 185 men (mean age 63 11) and 147 women (mean age 68 ± 10). A myocar- ial infarction before index examination was present in 42 men (77%) and 46 women (31%). The mean value f LV mass/height was 141 g/m in men and 111 g/m women. Mean LV diastolic diameter was 53 mm in en and 46 mm in women. Mean fractional shortening as 0.34 in men and 0.38 in women.

The prevalence rates of echocardiographic LV abnormalities in the study population are reported in Table II. Criteria for LV hypertrophy were fulfilled in 76 men (41%) and 76 women (52%), whereas high LV wall thickness was present in 80 men (43%) and 118 women (80%). The prevalence of LV dilatation was 43 of 185 in men (23%) and 28 of 147 in women (19%). Low fractional shortening occurred in 37 men (18%) and 16 women (11%). A combination of low fractional shortening and LV dilatation was present in 23 men (12%) and in 8 women (5%).

Cardiovascular disease events: During a mean follow-up of 3.90 years there were 99 new cardiovascular disease events in 60 men and 131 events in 58 women. Twenty-two men (12%) and 16 women (11%) sustained myocardial infarction.

During the follow-up period 49 men (26%) and 40 women (27%) died. Total cardiovascular mortality was 24 of 185 men (13%) and 25 of 147 women (17%).

The age-adjusted relative risks for new cardiovascular disease events according to a 1 standard deviation change for each of the continuous echocardiographic parameters are reported in Table III. After controlling for age in bivariate Cox proportional hazards models, LV systolic diameter was predictive of cardiovascular risk in men and women. Every 1 standard deviation increment in LV systolic diameter was associated with a relative risk of 1.28 in men (95% CI 1.02 to 1.63) and 1.40 in women (95% CI 1.09 to 1.82). Additionally, LV mass/height (RR = 1.25, 95% CI 1.01 to 1.55) in men and LV diastolic diameter (RR = 1.36, 95% CI 1.05 to 1.76) in women were predictive of cardiovascular risk.

TABLE III Age-Adjusted Relative Risk of New Cardiovascular Disease Events According to Continuous Echocardiographic Parameters

	Men			Women		
Parameter	Increment	RR	95% CI	Increment	RR	95% CI
LV mass/height	50 g/m	1.25	1.01–1.55	43 g/m	1.22	0.98–1.54
Septal wall thickness	4 mm	1.17	0.91–1.51	4 mm	1.17	0.92–1.50
Relative wall thickness	0.09	1.03	0.91–1.15	0.11	1.04	0.91–1.19
LV diastolic diameter	6 mm	1.15	0.93–1.43	5 mm	1.36	1.05–1.76
LV systolic diameter	6 mm	1.28	1.02–1.63	5 mm	1.40	1.09–1.82
Fractional shortening	−0.07	1.14	0.81–1.63	−0.05	1.16	0.89–1.51

Increments correspond to 1 SD change of the respective echocardiographic parameter.
CI = confidence interval; LV = left ventricular; RR = relative risk.

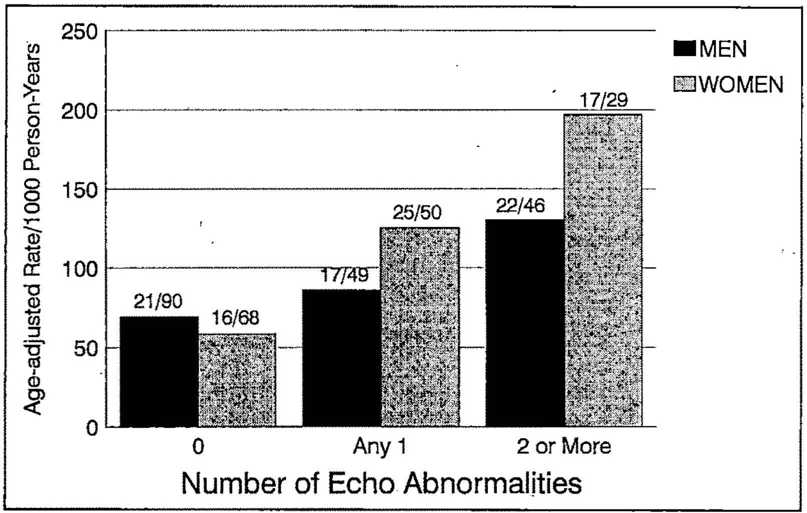

FIGURE 1. Age-adjusted incidence (per 1,000 person-years) of new cardiovascular disease events according to the presence of 0, 1 or ≥2 of the following echocardiographic abnormalities: (1) left ventricular hypertrophy; (2) reduced fractional shortening; and (3) increased end-systolic left ventricular diameter. ***Numbers above bars*** **represent the number of new events/the number of subjects at risk.**

TABLE IV Age-Adjusted Relative Risk of New Cardiovascular Disease Events According to Dichotomous Echocardiographic Variables

	Men		Women	
Variable	RR	95% CI	RR	95% CI
LV hypertrophy	1.30	0.78–2.17	2.30	1.29–4.12
High LV wall thickness	1.19	0.71–1.99	3.36	1.18–9.55
High relative wall thickness	1.07	0.79–1.44	1.30	0.99–1.70
LV dilatation	1.57	0.91–2.70	1.54	0.84–2.81
High LV systolic diameter	1.57	0.92–2.69	2.59	1.45–4.62
Low fractional shortening	1.91	1.11–3.31	1.91	0.90–4.05
Low fractional shortening + LV dilatation	2.13	1.13–4.02	3.25	1.28–8.25
Low fractional shortening + LV hypertrophy	1.87	0.99–3.53	2.19	0.99–4.85

Abbreviations as in Table III.

TABLE V Incidence of Cardiovascular Disease Events as a Function of the Presence of Echocardiographic Abnormalities*

No. of Abnormalities*	No. of Subjects at Risk	No. of Events	Age-Adjusted Event Rate Per 1,000 Patient-Years
	Men		
0	90	21	69.1
Any 1	49	17	85.8
≥2	46	22	130.1
	Women		
0	68	16	58.2
Any 1	50	25	125.2
≥2	29	17	196.9

*Based on the presence of the following echocardiographic abnormalities: left ventricular hypertrophy, reduced fractional shortening and increased end-systolic left ventricular internal diameter.

The age-adjusted relative risks for new cardiovascular disease events according to dichotomous echocardiographic variables are reported in Table IV. In men, low fractional shortening (RR = 1.91, 95% CI 1.11 to 3.3) and a combination of low fractional shortening with LV dilatation (RR = 2.13, 95% CI 1.13 to 4.02) were significant predictors of cardiovascular disease events. In women, cardiovascular disease risk was increased with LV hypertrophy (RR = 2.30, 95% CI 1.29 to 4.12), increased LV wall thickness (RR = 3.36, 95% CI 1.18 to 9.55), high LV end-systolic internal diameter (RR = 2.59, 95% CI 1.45 to 4.62) and a combination of low fractional shortening with LV dilatation (RR = 3.25, 95% CI 1.28 to 8.25).

The age-adjusted rates of new cardiovascular disease events according to the presence of 3 specified echocardiographic abnormalities are shown in Figure 1. In the absence of any of the 3 abnormalities the age-adjusted incidence (per 1,000 person-years) of cardiovascular disease was 69 in men and 58 in women (Table V). When ≥2 abnormalities were present, the corresponding rates were 130 and 197 for men and women, respectively.

DISCUSSION

LV function is a strong predictor of survival in patients with coronary artery disease[6,7] and after myocardial infarction.[8,9] Limited data exist regarding the association of LV mass with new morbid and fatal events in subjects with overt coronary disease.[10] On this basis, the present study was designed to examine the prognostic use of M-mode echocardiography in Framingham Heart Study subjects with clinically apparent coronary artery disease. The echocardiographic parameters were considered both as continuous and dichotomous variables, based on the partition values derived from a healthy reference population. The associations of echocardiographic measurements of LV structure and function with major morbid and fatal outcomes were examined.

Echocardiographic measurements of left ventricular structure and clinical outcome: Among LV structural variables, LV mass was predictive of new cardiovascular disease events in men. In women, LV hypertrophy, increased wall thickness and LV internal diameter (systolic and diastolic) were associated with the incidence of cardiovascular sequelae. Data from the Cook County Heart Disease Registry[10] demonstrated that LV mass and wall thickness measured by M-mode echocardiography were the most important predictors of survival in a cohort with coronary artery disease. However, these investigators excluded subjects with dilated hearts.

In men, LV mass was a statistically significant predictor of new cardiovascular disease events when considered as a continuous variable, whereas in women, LV mass achieved statistical significance only when considered as a dichotomous variable. In men the effect of LV mass on cardiovascular risk may be related in part to contributions of both LV thickness and diastolic internal diameter, although neither of the 2 components of echocardiographic LV mass alone achieved statistical significance. The predictive value of LV hypertrophy in women is slightly less than that of increased wall thickness, suggesting that increased LV wall thickness is a major determinant of adverse outcomes in women with coronary artery disease. However, the distribution of LV wall thickness values in the healthy reference population was narrow, producing an unusually low 95th percentile value for this variable. This resulted in fulfillment of increased LV wall thickness in 80% of women with coronary artery disease in our study and might have exaggerated the impact of this dichotomous variable on relative risks.

Echocardiographic measurements of left ventricular function and clinical outcome: The contributions of abnormal cardiac structure to outcome are linked to those of LV function by virtue of the inverse relation between measurements of systolic function (e.g., fractional shortening) and LV chamber size. Reduced fractional shortening is due to a poor LV contractile state and is associated with high LV systolic diameter, often combined with diastolic LV dilatation. In the present study, the prognostic impact of impaired LV systolic function on incidence of new cardiovascular disease events is evident in men (low fractional shortening) as well as in women (LV systolic diameter), confirming previous reports.[6-9]

In men, reduced fractional shortening and its combination with LV dilatation was predictive of recurrent cardiovascular events. The predictive value of reduced fractional shortening is attributable in part to both LV systolic and diastolic diameter. Although cardiovascular risk was increased only when LV end-systolic internal diameter was considered as a continuous variable, the combination of low fractional shortening with LV dilatation was a powerful predictor of outcome.

On the other hand, in women, the risk of new cardiovascular disease events was associated with LV end-systolic internal diameter, both as a continuous and as a dichotomous variable. The relative risk for new cardiovascular disease events was 1.40 for each standard deviation increment in LV systolic diameter and 2.59 for high LV systolic diameter. Of interest, angiographic LV end-systolic volume, which is analogous to M-mode echocardiographic LV end-systolic diameter, was identified in a recent study[9] as the major determinant of survival after myocardial infarction. Not surprisingly, the greatest cardiovascular risk was observed when low fractional shortening was associated with LV dilatation (RR = 3.25, 95% CI 1.28 to 8.25). This combination represents the concomitant presence of reduced contractility and increased LV size, reflecting abnormalities both of LV structure and function.

Study limitations: The most important technologic limitation of the present study involves the use of M-mode echocardiography in the presence of coronary artery disease, where regional wall motion abnormalities may exist.[18] Two-dimensional real-time imaging allowing direct visual guidance of M-mode acquisition,[19,20] only partially improves the reliability of LV measurements in these circumstances. Nevertheless, M-mode echocardiography has been used for large population-based epidemiologic purposes in subjects with prevalent coronary artery disease.[10] In the present study, M-mode echocardiography identified subgroups at increased risk for new cardiovascular disease events. The echocardiographic determinants of clinical outcome are consistent with predictive parameters obtained by techniques that evaluate the ventricle more completely in patients with coronary artery disease.[6-10,21-23]

Another limitation is the heterogeneity of baseline clinical features of the study population. Subjects with myocardial infarction and subjects with chronic myocardial ischemia, while sharing the same baseline pathology, are widely different in cardiac characteristics and prognosis. However, alterations of LV function and structure have a profound influence on outcome in both categories of subjects. Thus, it seems reasonable to have considered these 2 subsets of patients as a single cohort for the purposes of the present study.

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Risk Factor Correlates of Coronary Calcium as Evaluated by Ultrafast Computed Tomography

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Coronary artery calcium is invariably associated with atherosclerosis and has been linked to an increased risk of coronary events. Ultrafast computed tomography (CT) was recently used to document the presence and relative quantity of coronary calcium. The use of the self-reported coronary risk factors to identify persons with coronary calcium as documented by ultrafast CT screening was examined in 458 men and 139 women aged 26 to 81 years (88% asymptomatic). All subjects underwent ultrafast CT scanning, and received a questionnaire and underwent an interview regarding medical and risk factor history. Total calcium score was calculated as the sum of lesion-specific scores, each calculated as the product of density ≥130 Hounsfield units and area ≥0.51 mm^2. The prevalence of coronary calcium increased significantly ($p < 0.01$) by age group, and the greater the number of risk factors present, the greater the likelihood of calcium. From multiple logistic regression, age ($p < 0.01$), male sex (relative risk [RR] 3.03; $p < 0.01$), and history of smoking (RR 1.85; $p < 0.01$) and hypertension (RR 1.65; $p < 0.05$) were independently associated with the probability of detectable calcium. Among asymptomatic subjects, an association with hypercholesterolemia was also seen (RR 1.56; $p < 0.05$). The results demonstrate that cardiovascular risk factors can help in identifying the likelihood of coronary calcium.

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Despite decreasing mortality rates, coronary artery disease remains the major cause of death among Americans.[1,2] Accurate diagnosis has been limited to either invasive methods, such as coronary angiography, or noninvasive methods, such as exercise treadmill testing that has significant false-positive and false-negative rates.[3,4] The ability of the standard risk factor profile to predict clinical coronary events is also limited.[5]

Coronary calcium deposits have been documented histologically to be a frequent component of atherosclerotic plaque.[6–9] Patients with radiographically detectable calcium have also been shown to be associated with as high as a fourfold increase in mortality compared with those without coronary calcium.[10] Although digital subtraction fluoroscopy provides a sensitive means to detect coronary calcium,[11] ultrafast computed tomography (CT) is probably more sensitive and is capable of quantitating relative amounts of coronary calcium. Furthermore, it is highly specific for the detection of nonobstructive[12] as well as obstructive[13] angiographic disease, and enables rapid image acquisition, the elimination of cardiac motion artifacts, and high-contrast resolution. Noninvasive ultrafast CT may, in conjunction with known risk factors, improve the sensitivity of identifying subjects at risk for coronary artery disease events. To determine which subjects are most likely to have coronary artery calcium by ultrafast CT, we evaluated the contribution of self-reported cardiovascular risk factors to predicting presence and extent of calcification.

METHODS

Study population and interview: The study group included 458 men and 139 women (age range 26 to 81 years, mean 52 ± 10; 84% asymptomatic and 7% with previously reported myocardial infarction), primarily self-referred (or by their physician) to a private medical clinic, who were consecutively studied between May 1991 and March 1992 by ultrafast CT coronary artery scanning. In general, these patients constituted a high-risk subset of the general population (53% of subjects had ≥2 reported risk factors). A questionnaire was given to all patients, which included questions regarding medical and risk factor history, including items on history of systemic hypertension, diabetes mellitus, hypercholesterolemia, chest pain suggestive of angina pectoris (by Rose questionnaire), myocardial infarction and tobacco use, and family history of premature (aged ≤55 years in a parent or sibling) myocardial infarction. A physician reviewed the completed responses with each subject to ascertain completeness and validity.

Procedures for ultrafast computed tomography: All studies were performed with a standard protocol previ-

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TABLE I Mean ± SE Total Calcium Score and Prevalence of Detectable Calcium (score > 0) by Age Group

Age (year)	Mean ± SE (n)		Score >0	
	Men	Women	Men	Women
<40	7 ± 5 (47)	0.1 ± 0.1 (8)	11%	13%
40–49	55 ± 17 (140)	10 ± 4 (42)	44%	29%
50–59	155 ± 26 (158)*	20 ± 7 (52)	70%	29%
60–69	362 ± 63 (20)†	71 ± 30 (6)‡	90%	67%
≥70	1,051 ± 245 (20)†	70 ± 57 (6)	90%	67%
Overall	191 ± 22 (458)§	29 ± 8 (139)	5,990	3,990

*p <0.05 compared with patients aged <40 and 40 to 49 years; †p <0.001 compared with all other groups; ‡p <0.05 compared with ages 50 to 59 years, and p <0.01 compared with ages 40 to 49 years; §p <0.001 compared with women.

ously described,[2] using an Imatron C-100 ultrafast CT scanner. Briefly, this involved subjects being positioned supine, head first, into the scanning aperture with no couch angulation, and instructed to take 3 deep breaths and hold their breath (at end-expiration) while a preview scan was performed. Positioning of the patient was checked and, if necessary, adjusted so that scanning began from near the lower margin of the bifurcation of the main pulmonary artery. Coronary visualization was achieved without contrast by using the high-resolution volume mode of the ultrafast CT scanner in conjunction with a 100 ms scan time, 3 mm slice thickness, electrocardiographic triggering (to 80% of the RR interval), and breath-holding for approximately 45 seconds. Twenty contiguous slices were obtained with no interslice gaps. Each of 20 levels (which encompassed the proximal portions of the coronary arteries where nearly all calcium is present)[12] were evaluated sequentially to determine presence and quantity of coronary calcium. From the established protocol,[12] the threshold for a calcified lesion was set at a CT density of 130 Hounsfield units and an area ≥0.51 mm^2. At each level, all pixels with a CT density ≥130 were displayed. A region of interest was manually encircled around each visible lesion within each coronary artery, and computer-acquired measurements of lesion area (mm^2) and maximal Hounsfield number of each region of interest were recorded. A lesion score was determined based on maximal Hounsfield number in the following manner: 1 = 130 to 199; 2 = 200 to 299; 3 = 300 to 399; and 4 = >400 Hounsfield units. A score of each region of interest was calculated by multiplying density score by area. A total calcium score was determined by adding each of these scores for all 20 slices. Total scores were also obtained for each of the following major coronary arteries: left main, left anterior descending, left circumflex and right.

Statistical analysis: Mean calcium score and prevalence of detectable calcium (total calcium score >0) were calculated initially for men and women separately across age groups (<40, 40 to 49, 50 to 59, 60 to 69 and ≥70 years). Analysis of variance and chi-square analyses were used (as appropriate) to examine age-related differences.

For men and women separately, the chi-square test was used to compare the proportions of subjects with detectable calcium (as defined previously) by reported history of high blood pressure, hypercholesterolemia, diabetes, chest pain and myocardial infarction (confirmed by physician), family history of premature (aged <55 years) myocardial infarction in sibling or parent, and any previous tobacco use. Mean calcium score and prevalence of detectable calcium were also compared for subjects with 0, 1, 2, 3, 4 or more principal risk factors (high blood pressure, hypercholesterolemia, diabetes, smoking or positive family history) by analysis of variance or chi-square analyses, as appropriate.

Stepwise multiple logistic regression analysis was used to examine the independent relation of each of the aforementioned potential risk factors (except previous infarction, which was not considered as a candidate variable, because it clinically indicates the presence of disease) to the probability of having calcium after adjusting for the effects of age, sex and other medical history and risk factor variables. Separate analyses were performed for all subjects (n = 597) and the subset who were asymptomatic and without previous myocardial infarction (n = 493). Alpha values of 0.15 and 0.10 were required for a variable to enter and remain, respectively, in the regression model.

RESULTS

The prevalence of detectable calcium varied significantly (p <0.01) by age group for both men and women (Table I). Mean calcium scores also increased by age group, although more significantly in men (p <0.01) than women (p = 0.03). There was a large increase in the prevalence of detectable calcium in men between the 40 to 49 year (44%) and 50 to 59 year (70%) age groups and in women between the 50 to 59 year (29%) and 60 to 69 year (71%) age groups. Whereas almost 90% of patients aged <40 years had no calcium, only a few subjects (10% of men) aged >70 had no calcium.

Hypercholesterolemia or family history of premature myocardial infarction were the most frequently reported risk factors in the patient population, each occurring in approximately half of subjects. A significantly higher prevalence of detectable calcium was found in men with than without diabetes, hypertension, previous smoking, reported history of chest pain, or previous myocardial infarction (p <0.05) (Table II). In women, the prevalence of detectable calcium was significantly greater in those with than without a reported history of hypercholesterolemia (p <0.05) or smoking (p <0.05).

There was a significant (p <0.01), continuous, graded relation of mean calcium score and prevalence of detectable calcium with an increasing number of risk factors in men (Table III). In men with no risk factors, prevalence of calcium was 37.8%, which doubled to 76% in those with ≥4 risk factors. A significant (p <0.01) relation between prevalence of calcium and number of risk factors was found in both men and women.

Table IV shows the results from multiple logistic regression analyses. Among all subjects, age, male sex, previous smoking, and high blood pressure were all independently associated with a significant (p <0.01 or <0.05) increased probability of detectable calcium. Men had 3 times (RR 3.03; p <0.01) the likelihood of having detectable calcium than did women. Subjects

TABLE II Prevalence of Detectable (calcium score > 0) and Significant Calcium by Self-Reported Cardiovascular Risk Factors

Risk Factor (% of men; women with risk factor)		Detectable Calcium (%) Men (n = 458)	Women (n = 139)
Hypercholesterolemia	Yes	64%*	47%†
(52.2; 54.7)	No	55%	29%
Diabetes	Yes	81%†	56%
(5.7; 6.5)	No	58%	38%
Hypertension	Yes	75%‡	44%
(25.1; 18.0)	No	54%	34%
Previous smoking	Yes	70%‡	54%‡
(36.7; 25.2)	No	53%	34%
Family history of premature MI	Yes	63%	42%
(45.9; 48.2)	No	56%	36%
Current chest pain	Yes	74%†	32%
(12.5; 15.8)	No	57%	40%
Previous MI	Yes	94%‡	50%
(7.0; 1.4)	No	57%	39%
Body mass index (kg/m^2)	Yes	26 ± 3	25 ± 3
(mean ± SD) by calcium status	No	26 ± 3	25 ± 4

*$p < 0.10$; †$p < 0.05$; ‡$p < 0.01$ compared with subjects without indicated risk factor (except for body mass index, where comparison is with those without calcification).
MI = myocardial infarction.

with history of smoking had an 85% increased risk (RR 1.85; $p < 0.01$), and those with high blood pressure had a 65% increased risk (RR 1.65; $p < 0.05$). Analyses obtained among the subset of subjects who were asymptomatic and without previous infarction showed history of hypercholesterolemia also predictive (RR 1.56; $p < 0.05$), but found a weaker relation with hypertension.

DISCUSSION

Important relations between cardiovascular risk factors and coronary artery disease as documented by coronary angiography have been the subject of previous investigations.[5,14] This is the first report from a large cohort of patients that examines the association of coronary atherosclerosis detected noninvasively by ultrafast CT calcium screening with a wide spectrum of cardiovascular risk factors.

The strong positive correlation of age with prevalence of coronary calcium in men and women, as well as the higher prevalence of calcium in men (59.4 vs 38.9%; $p < 0.01$), is consistent with clinical data reported by other investigators.[15] However, it is not known whether the prognostic significance of coronary calcium diminishes with age. Long-term follow-up studies are needed to establish this.

History of hypercholesterolemia was independently associated with coronary calcium prevalence in asymptomatic subjects with no previous infarction. Self-reported history, rather than actual venepuncture-assessed lipid levels, may be more appropriate to use in subjects receiving lipid-lowering medications that would have lowered actual levels. Such patients may have had hyperlipidemia for many years. Other investigators have also shown coronary calcium to be associated with total (Detrano et al, unpublished observations) or low-density lipoprotein[15] cholesterol, which is consistent with our findings.

TABLE III Mean ± SE Calcium Score and Prevalence (%) of Detectable (total score > 0) and Significant (total score ≥ 50) Calcification by Number of Risk Factors

No. of Risk Factors*	Men		Women	
0	109 ± 33 (82)	38%	6 ± 4 (22)	23%
1	143 ± 41 (129)	57%	32 ± 18 (47)	28%
2	188 ± 35 (139)	62%	26 ± 9 (49)	53%
3	275 ± 56 (83)	75%	62 ± 31 (17)	35%
≥4	442 ± 171 (25)	76%	29 ± 14 (4)	100%
	$p < 0.01$	$p < 0.0001$	$p = 0.45$	$p < 0.01$

*Including reported history of high cholesterol and blood pressure, smoking and premature (aged ≤55 years) myocardial infarction.
p values indicate significance of test comparing means or prevalences across all risk factor categories.

TABLE IV Multiple Logistic Regression Analyses Evaluating Association of Cardiovascular Risk Factors to Probability of Detectable (score > 0) Calcium in All Subjects (n = 597), and in Those Asymptomatic and Without Previous Infarction (n = 493)

	All Subjects		Asymptomatic, No MI	
Risk Factor	Coefficient	RR	Coefficient	RR
Age (year)	0.11	1.12*	0.11	1.11*
Sex (women/men)	−1.11	3.04*†	−1.95	2.59*†
Previous smoking	0.61	1.85*	0.45	1.57‡
Hypercholesterolemia	0.35	1.42§	0.45	1.56‡
Hypertension	0.50	1.65‡	0.47	1.59§
Family history of premature MI	0.34	1.40		

*$p < 0.01$; ‡$p < 0.05$; §$p < 0.10$.
†Relative risk for men compared with women.
MI = myocardial infarction; RR = relative risk.

Diabetes was significantly associated with detectable calcium only in men by univariate analysis. The greater prevalence of calcium in diabetic patients is consistent with that reported previously from an autopsy series.[16]

History of hypertension was also associated with an increased probability of detectable calcium (but only in the entire cohort), conferring a 65% increased probability from multiple logistic regression analysis adjusted for other factors. This may relate to the finding that hypertension can aggravate the atherosclerotic process through arterial wall trauma.[17-19] Although we did not obtain actual resting blood pressures, a self-reported history of using antihypertensive medication may be more relevant to our study, because a number of subjects were currently controlled on antihypertensive medication.

Previous tobacco use was the strongest indicator, other than age or gender, for detectable calcium in both men and women. This was associated with an approximately two-fold increased probability of calcium in multivariate analysis. It has also been reported that tobacco use correlates with arterial atherosclerosis in autopsied men.[20]

History of myocardial infarction was also found to be associated with detectable calcium in men. If history of myocardial infarction (confirmed by treating physician) is used as the gold standard for coronary artery disease, this indicates a sensitivity in our study of 94% in men (30 of 32 with a previous infarction had calcification). Among subjects with current chest pain, 74% of men but only 32% of women had calcium in their arteries, possibly reflecting a lower prevalence of actual disease in women than in men with chest pain.

Finally, we noted that the mean calcium score and prevalence of detectable calcium in men and women increases in a graded fashion with the number of risk factors. Lee et al[15] also reported significantly greater calcium scores among patients with ≥3 risk factors than among those with ≤2.

The search for effective screening strategies for coronary artery disease is hampered by the imperfect sensitivity and specificity of currently available tests. Testing based on functional assessment has a reasonably good predictive value, but depends on the presence of significant coronary luminal narrowing for diagnosis and is therefore not useful for early detection of subclinical coronary artery disease in high-risk subjects.[3,4] Furthermore, it is now recognized that a significant proportion of myocardial infarctions are due to rupture of nonobstructive atherosclerotic plaques that would not be detected by any functional test.[21] Detection of calcium by fluoroscopy or nongated CT has been used as a screening test for coronary artery disease, but has limited sensitivity.[11,22,23] In contrast, ultrafast CT is more sensitive for detection of coronary calcium. Recent studies with ultrafast CT showed an excellent correlation between quantification of coronary calcium and angiographic extent of coronary artery disease.[13,24,25] Whether this sensitivity can be further enhanced by choosing a lower Hounsfield number (<130) for detection of possibly early calcific lesions needs further investigation.

Current strategies for detecting patients at increased risk of clinical events are based on screening for multiple risk factors. Although this strategy defines cohorts of patients with increased risk, it has poor predictive value when applied to an individual patient, because many subjects with the risk factor may never develop clinically evident coronary artery disease (unpublished observations). Larger prospective studies are needed to determine whether calcific deposits defined by ultrafast CT coronary artery scanning in combination with known risk factors can better enable physicians to evaluate subsequent risk of coronary events.

Until these data are available, we believe that patients with concomitant risk factors and prevalent coronary calcium could be targeted for more aggressive risk factor intervention to retard any likely progression of disease.

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Circulating Aggregated Platelets, Number of Platelets per Aggregate, and Platelet Size During Acute Myocardial Infarction

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Circulating aggregated platelets (total, reversibly and irreversibly aggregated), the number of platelets per aggregate and "big" platelets were measured by a modification of the Wu and Hoak method in 42 patients on the first, second and fifth day of acute myocardial infarction (AMI). Among them, 30 had an uncomplicated course and 12 patients had complications that occurred between the 5th and 10th day of hospitalization (7 patients had reinfarction and 5 died). In all patients the measured parameters were elevated compared with those of control subjects. There was a significant increase, especially after the first observation day, in the values of total aggregated platelets (37 ± 11% vs 26 ± 12%, $p < 0.001$), reversibly aggregated platelets (27 ± 9% vs 17 ± 8%, $p < 0.001$) and the average platelets per aggregate (8.6 ± 0.3 vs. 2.3 ± 0.4) in patients with versus without complications. In considering the role of platelets in the development of AMI, these findings may add information to the role of platelets in determining the course of AMI.

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Previous studies[1-11] have emphasized the role of platelets in the development and course of acute myocardial infarction (AMI). Colman[5] suggested that platelets have a central role in coronary thrombosis through releasing thromboxane A_2, causing coronary vasoconstriction and platelet aggregation. AMI was induced in animals by infusing adenosine diphosphate which provoked platelet aggregation in the microcirculation.[8] Other investigators[1-4] found an increased number of platelet aggregates in the myocardial microcirculation of patients who died suddenly of coronary artery disease. An increased number of circulating aggregated platelets, mostly in the reversible form, were also found in patients with AMI.[6] The number of platelets per aggregate was also emphasized in patients with ischemic heart disease.[12] Trowbridge,[13] Cameron[14] and Martin[15] and their co-workers found an increase in platelet size in patients with AMI, and hypothesized that these big platelets may be involved in the development of AMI. This study examines platelet function parameters during AMI.

METHODS

The study group included 42 patients (30 men and 12 women, mean age 60 years [range 28 to 84]) hospitalized in our department of internal medicine and coronary care unit. All patients had AMI which was diagnosed according to World Health Organization criteria. All patients received 5 mg of isosorbide dinitrate sublingually during pain. Twelve patients received heparin (30,000 U/day) and 10 patients propranolol (40 to 80 mg/day). Eight patients had a previous AMI, 13 patients had hypertension and 7 had hypercholesterolemia. Diabetic patients were not included in the study. Twenty healthy volunteers (14 men and 6 women, mean age 57 years [range 28 to 75]) served as daily reference control subjects. Blood samples (anticoagulated with ethylenediaminetetraacetic acid) were drawn on the first 24 hours of admission and on the second and fifth day of hospitalization. The percentage of circulating aggregated platelets, as well as reversibly and irreversibly aggregated platelets, were measured microscopically by a modification of the Wu and Hoak method described elsewhere.[6] The average platelets per aggregate was calculated by dividing the number of platelets forming aggregates by the number of aggregates per 1,000 counted platelets.[12] The percentage of big platelets was determined microscopically on the same slide that served for the determination of the percentage of circulating aggregated platelets in the solution containing formaldehyde. Platelets were defined as big when their diameter exceeded half of the diameter of adjacent erythrocytes.

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TABLE I Platelet Function Parameters in 42 Patients on the First, Second and Fifth Days of Acute Myocardial Infarction

	Day of Hospitalization	Control Value	Acute Myocardial Infarction	
			Uncomplicated (n = 30)	Complicated (n = 12)
Aggregated platelets (%)	1	6.5 ± 1.9	24 ± 9	25 ± 7
	2		26 ± 12	* 37 ± 11
	5		18 ± 11	* 36 ± 10
Irreversibly aggregated platelets (%)	1	4.1 ± 2.0	10 ± 4	11 ± 5
	2		10 ± 3	* 8.4 ± 3.1
	5		12 ± 3	7.9 ± 2.8
Reversibly aggregated platelets (%)	1	2.1 ± 1.0	12 ± 7	* 14 ± 7
				*
	2		17 ± 8	* 27 ± 9
	5		9.6 ± 7.3	* 29 ± 6
Average platelets per aggregate	1	2.2 ± 0.3	2.5 ± 0.3	* 3.2 ± 0.4
				*
	2		2.3 ± 0.4	* 8.6 ± 0.3
				*
	5		2.3 ± 0.3	* 3.3 ± 0.2
"Big" platelets (%)	1	9.9 ± 2.5	18 ± 4	20 ± 5
	2		19 ± 4	18 ± 5
	5		19 ± 4	19 ± 5
Platelet count 3 (× 10 mm)	1		362 ± 71	* 399 ± 52
	2	150–400	205 ± 82	* 386 ± 99
	5		216 ± 103	* 391 ± 101

*$p < 0.05$.
Values are expressed as mean ± SD.

Blood samples were taken between 8 and 10 A.M. while patients were in the recumbent position. All measurements were obtained in triplicate and daily results were closed to the technicians and the co-author who was in charge of blood sampling.

Statistical methods: Mean ± standard deviation was calculated for the studied variables. Comparisons of variables between the observation days and in several clinical subgroups were determined by using the Mann-Whitney U-Wilcoxon rank-sum test. Spearman's coefficients were used for correlation.

RESULTS

Clinical follow-up: During the observation period, 30 patients had an uncomplicated and 12 patients a complicated course. Of these 12 patients, 5 died between the fifth and eighth day of follow-up and 7 developed reinfarction. The causes of death were cardiogenic shock in 3 patients and myocardial rupture in 2 (diagnosed by autopsy). Reinfarction occurred between the sixth and tenth day of follow-up, diagnosed by reappearance of typical cardiac pain and electrocardiographic ST-T changes (3 patients) or new Q waves on the electrocardiogram (4 patients) and reelevation of cardiac enzymes ≥50% from their last value (all 7 patients).

Total aggregated platelets (Table I): This parameter was elevated in both groups. However, on the second and fifth days the complicated group had a significantly higher percentage of total aggregated platelets.

Irreversibly aggregated platelets (Table I): Although elevated in both groups compared with the reference value, a gradual (although not significant) decrease in irreversibly aggregated platelets in the complicated group on the second and fifth days of AMI was observed.

Reversibly aggregated platelets (Table I): This parameter was significantly increased in both groups. However, a significant increase in this parameter was observed in the complicated versus the uncomplicated group on the first, second and fifth days of AMI. There was a significant increase in this parameter in the complicated group between the first and second days, persisting until the fifth day. In the uncomplicated group reversibly aggregated platelets decreased toward the fifth day.

Average platelets per aggregate (Table I): This index was elevated significantly in both groups, especially in the complicated one on each studied day. In the complicated group there was a significant increase in the average platelets per aggregate between the first and second day, decreasing between the second and fifth day.

Big platelets (Table I): Both groups had an elevated percentage of big platelets in all the studied days with no differences between the 2 groups or between the studied days in each group.

DISCUSSION

This study documented the variations in some platelet function parameters during AMI. Although all patients with AMI had disturbances in the measured parameters during the first days of AMI (Table I), these disturbances were especially marked in patients who developed complications later. These findings may lead one to hypothesize about the role of platelets not only in the development of AMI, but also in the development of complications during AMI. This hypothesis should be further tested. The increase in total circulating aggregated platelets, especially reversible ones, has been emphasized and discussed previously.[6] The possible pathogenetic role of reversibly aggregated platelets in complications of AMI is that by being more active they may adhere more easily to a preexisting coronary thrombus or may undergo irreversible activation on a coronary lesion and form downstream platelet aggregates, mainly in the coronary microcirculation; this may explain later complications in the course of AMI.[2-4] The average platelets per aggregate, which can estimate the potential mean platelet aggregate size, was increased in patients with AMI especially in patients who developed complications (Table I). This parameter may reflect the ability of platelets to form aggregates of varying size through a fixed circulation distance (palm-cubital). A strong correlation (r = 0.9) was found between the average platelets per aggregate and reversibly aggregated platelets, indicating that these platelets could form aggregates containing more platelets and, thus, an increased obstructive potential (explaining one of their pathophysiologic roles in AMI complications). A significant correlation (r = 0.47) was also found between the average platelets per aggregate and the percentage of big platelets. A persistent elevation of big platelets was found similarly in both studied groups during the study period. Previous studies,[13-15] as well as the present one, emphasized the role of larger-sized platelets in the development of AMI. Our study during the first 5 days of AMI showing similar values in both groups may lead one to doubt the role of big platelets in AMI complications. The origin of platelet disturbances during AMI is beyond the scope of this study. However, stress and catecholamine release during AMI could certainly contribute to platelet activity. Another possibility was raised by Martin et al,[15] who suggested that big platelets originated in the pulmonary circulation due to an increase in megakaryocyte deoxyribonucleic acid content. One can speculate about the possible effect of drugs taken by patients on the studied parameters. Because both groups were treated similarly, we can indirectly neutralize this factor; however, further studies are needed to clarify this issue. In summary, an association between platelet function disturbances (measured ex vivo) and AMI complications was demonstrated, and warrants further clarification.

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Effects of Simulated Left Bundle Branch Block on QRST Time-Integral Values of 12-Lead Electrocardiograms in Patients With and Without Prior Anterior Wall Myocardial Infarction

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The effects of right ventricular pacing, which simulated left bundle branch block (BBB), on QRST time-integral values of 12-lead electrocardiograms (ECGs) were examined, and the clinical usefulness of QRST values for estimating the severity of left ventricular wall motion abnormalities due to a prior anterior wall myocardial infarction (MI) in the setting of left BBB were evaluated. Digitized ECGs were recorded during normal sinus rhythm and simulated left BBB in 38 patients (24 with and 14 without prior anterior wall MI). QRST values were calculated in each lead point of 12-lead ECGs. Data from 608 normal subjects were used as control values; the mean ± 2 SD of these values was regarded as the normal range. The parameter ΣDE was defined as the sum of the differences between the normal mean QRST value and the QRST values of a given patient in leads where the QRST value was less than the normal range. The correlation coefficient of ΣDE for the 2 activation sequences was highly significant. Although small but significant changes were seen in QRST values in leads I, II, III, aVR, aVF and V_1 during simulated left BBB, left precordial leads showed no significant changes in QRST values. A criterion of ΣDE >40 mV · ms for detecting an anterior wall MI showed a sensitivity of 88%, a specificity of 93%, and a diagnostic accuracy of 89%. The ΣDE was significantly ($p < 0.001$) correlated with the asynergy index calculated from left ventriculograms. The results show that simulated left BBB has little effect on QRST values of 12-lead ECGs, especially in left precordial leads, and that the QRST values may provide clinically useful information for detecting the presence of MI and estimating the severity of left ventricular wall motion abnormalities in patients with a prior anterior wall MI in the setting of left BBB.

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It is difficult to detect the presence and severity of anterior wall myocardial infarction (MI) in the presence of a complete left bundle branch block (BBB) by standard 12-lead electrocardiograms (ECGs).[1,2] Although various criteria to improve the ability of ECGs to diagnose MI complicated by left BBB have been proposed,[1–4] their diagnostic accuracy remains unsatisfactory.[2] Wilson et al[5] introduced the concept of ventricular gradient, according to which QRST areas from bipolar limb leads are largely independent of the activation sequence and dependent on repolarization properties. Abildskov et al[6] demonstrated that this concept is applicable to QRST isointegral maps recorded from unipolar leads with Wilson's central terminal. Burgess et al[7] reported that these maps reflect the extent and severity of repolarization abnormalities independent of activation sequence. These findings suggest that this concept is applicable to QRST time-integral values of 12-lead ECGs and that QRST values from unipolar leads reflect the severity of repolarization abnormalities. It has been reported that QRST isointegral maps and values from 12-lead ECGs are useful in detecting old MI with abnormal ventricular activation, such as left BBB and Wolff-Parkinson-White syndrome.[8–11] However, there have been no reports concerning the detection of severity of left ventricular wall motion abnormalities due to MI in the presence of left BBB by 12-lead ECGs. Small but significant effects of activation sequences on repolarization properties were recently demonstrated.[12,13] This study was designed to determine whether QRST values of 12-lead ECGs provide information useful for quantifying severity of left ventricular wall motion abnormalities due to anterior wall MI complicated by left BBB and whether QRST values can be used to detect the presence of anterior wall MI in patients with left BBB. Furthermore, we attempted to clarify which leads have significant effects on QRST values during simulated left BBB compared with supraventricular complex.

METHODS

Patients: Thirty-eight patients (35 men and 3 women, mean age 58.7 years, range 43 to 72) who underwent left ventriculography and coronary arteriography at the Anjo Kosei Hospital fulfilled the following selection criteria for this study: (1) digitized 12-lead ECGs recorded during sinus rhythm and right ventricular pacing, which simulated left BBB; (2) heart rate between

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50 to 90 beats/min; (3) clinically verified prior anterior wall MI or the absence of any prior MI; (4) no conduction disturbance; (5) no congenital heart disease; (6) no cardiomyopathy; (7) no valvular heart disease; and (8) no severe hypertension. MI was diagnosed by history of typical chest pain, serum enzyme changes and typical electrocardiographic changes during the acute phase of MI, and by a significant lesion found on coronary arteriography. Twenty four patients (23 men and 1 woman, mean age 60 years, range 43 to 72) had a prior MI, whereas the other 14 (12 men and 2 women, mean age 57 years, range 48 to 71) had no prior MI. Informed consent was given by all subjects before entry in the study.

Cardiac catheterization: Left ventriculography was recorded at 30 frames/s on 35 mm film using a Philips 6-inch image intensifier system (Cardiodiagnost). Left ventricular ejection fraction was calculated from left ventriculography, according to the area-length method of Sandler and Dodge.[14] Left ventricular wall motion was evaluated qualitatively, according to the reporting system of the American Heart Association,[15] by observers without knowledge of electrocardiographic data. Regional left ventricular wall motion was graded as follows: normal = 0; hypokinesia = 1; akinesia = 2; and dyskinesia = 3. The following 7 segments were scored separately: anterobasal, anterolateral, apical, diaphragmatic, posterobasal, septal and posterolateral. The asynergy index was calculated by adding the 7 scores. Coronary arteriography was performed by Sones' or Judkins' technique, and significant stenosis was defined as $\geq 75\%$ reduction in the luminal diameter of the coronary artery. All patients underwent coronary arteriography and left ventriculography within 8 hours of having ECGs recorded. All drugs were discontinued 2 days before ECGs were recorded.

Right ventricular pacing: After ECGs were recorded during sinus rhythm, a bipolar 6Fr pacing catheter was positioned in the right ventricle through the femoral or brachial vein. The right ventricle was paced with 1 ms square-wave pulses at twice the threshold voltage. The cycle length of right ventricular pacing was regulated so that it was slightly less than the spontaneous sinus cycle length. Right ventricular pacing simulating left BBB was maintained for ≥ 3 minutes before ECGs were recorded.

Digitized standard 12-lead electrocardiograms: Digitized 12-lead ECGs were recorded with the VCM-3000 system (Chunichi Denshi Company, Japan) to calculate QRST values. Because the details of data acquisition and processing were reported previously,[10,16] we will describe them only briefly. Unipolar ECGs were recorded simultaneously with reference to Wilson's central terminal. Frank X, Y and Z ECGs were also recorded simultaneously. Electrocardiographic data were scanned by multiplexers, digitized by analog/digital converters at a rate of 1,000 samples/s and stored on floppy disks. Two-point baseline adjustment was performed by choosing the flat portion of the TP segment before P and after T deflection of the selected PQRST complex. After baseline adjustment, a root-mean-square voltage versus time curve (based on X, Y and Z leads) was plotted to help identify the beginning of QRS and end of T deflection, which were manually selected from this curve. QRST deflection area was calculated by integrating each lead over the appropriate interval (expressed in mV • ms). Data sampling was performed at the expiratory level with the subject in the supine position. Correlation coefficients were calculated to quantify similarities between QRST areas of the 2 activation sequences. Paired *t* test was performed to identify small but statistically significant differences in QRST value at each lead between the 2 activation sequences.

The mean and SD of the normal QRST for each lead point were calculated from the data of 608 normal subjects (376 men and 232 women; mean age 42 years, range 17 to 81) whose chest X-rays, ECGs and physical examinations were normal. Data from normal subjects were provided by courtesy of the Task Force Committee of the Japanese Circulation Society for Body Surface Mapping.[17] To estimate the deviation of patient data from the normal values, the departure index (DI) for each lead was calculated with the VCM-3000 as follows: $DI = (X - mean)/SD$, where X represents the QRST at the corresponding lead for each patient.[18] Because we were interested in the decrease in QRST values, leads where DI values were <2 were designated as abnormally low QRST leads. The ΣDE parameter was derived from the abnormally low QRST leads and was defined as the sum of the values obtained by subtracting the QRST values of a given patient in each abnormally low QRST lead from the normal mean QRST value.

Statistical analysis: Correlations between electrocardiographic data and left ventriculographic findings were assessed by the least-squares method of linear regression analysis to determine the correlation coefficient. The diagnostic ability to identify the severity of left ventricular wall motion abnormalities in the simulated left BBB with ΣDE derived from the discriminant analysis was tested. Sensitivity, specificity and diagnostic accuracy were determined and expressed as a percentage. A relative, cumulative frequency distribution was used to determine the diagnostic criteria for detect-

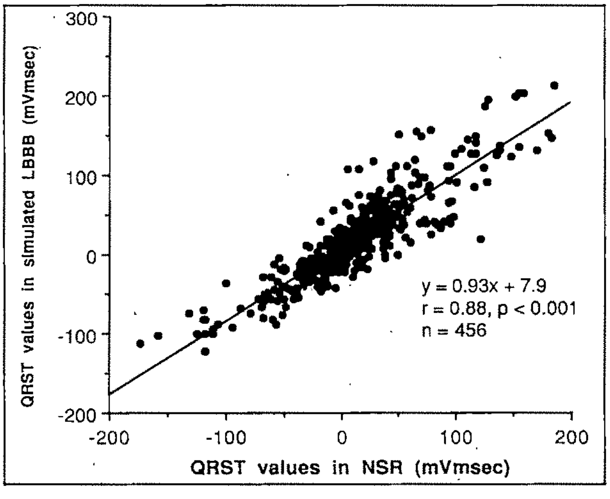

FIGURE 1. Correlation between QRST values of 456 lead points in 38 patients during normal sinus rhythm (NSR, supraventricular complex) and simulated left bundle branch block (LBBB).

TABLE I Comparison of QRST Values During Sinus Rhythm and Right Ventricular (RV) Pacing in 14 Patients Without Prior Myocardial Infarction

	QRST Values (mV · ms)			QRST Values (mV · ms)	
Lead	Sinus	RV Pace	Lead	Sinus	RV Pace
I	31 ± 12	31 ± 13	V_1	2 ± 19	−2 ± 18
II	41 ± 17	61 ± 21*	V_2	57 ± 50	65 ± 50
III	7 ± 20	27 ± 23*	V_3	92 ± 60	107 ± 68
aVR	−36 ± 11	−46 ± 14†	V_4	84 ± 51	91 ± 64
aVL	11 ± 12	2 ± 14	V_5	80 ± 38	82 ± 52
aVF	24 ± 18	43 ± 21*	V_6	61 ± 24	65 ± 33

*p <0.01; †p <0.05 versus sinus.
Values are mean ± SD.

TABLE II Comparison of QRST Values During Sinus Rhythm and Right Ventricular (RV) Pacing in 24 Patients With Prior Myocardial Infarction

	QRST Values (mV · ms)			QRST Values (mV · ms)	
Lead	Sinus	RV Pace	Lead	Sinus	RV Pace
I	7 ± 14	14 ± 13*	V_1	−8 ± 28	−16 ± 26†
II	24 ± 34	39 ± 32†	V_2	−17 ± 63	−6 ± 61
III	14 ± 32	23 ± 32*	V_3	−31 ± 81	−17 ± 69
aVR	−15 ± 19	−25 ± 19†	V_4	−17 ± 64	−8 ± 56
aVL	−3 ± 19	−4 ± 18	V_5	14 ± 43	22 ± 37
aVF	19 ± 33	30 ± 32†	V_6	30 ± 30	34 ± 28

*p <0.05; †p <0.01 versus sinus.
Values are mean ± SD.

TABLE III Comparison of QRST Values During Sinus Rhythm and Right Ventricular (RV) Pacing in 38 Patients With and Without Prior Anterior Myocardial Infarction

	QRST Values (mV · ms)			QRST Values (mV · ms)	
Lead	Sinus	RV Pace	Lead	Sinus	RV Pace
Total 12-lead	15 ± 50	20 ± 52			
I	15 ± 17	19 ± 15*	V_1	−4 ± 25	−10 ± 24†
II	30 ± 30	46 ± 30†	V_2	10 ± 68	19 ± 66
III	12 ± 28	24 ± 29†	V_3	13 ± 95	28 ± 91
aVR	−21 ± 20	−32 ± 20†	V_4	19 ± 77	28 ± 76
aVL	1 ± 18	−2 ± 17	V_5	38 ± 52	43 ± 52
aVF	21 ± 28	35 ± 29†	V_6	41 ± 32	45 ± 33

*p <0.05; †p <0.01 versus sinus.
Values are mean ± SD.

TABLE IV Mean ± SD of QRST Values of Each Lead Point in 608 Normal Subjects

Lead	QRST Values (mV · ms)	Lead	QRST Values (mV · ms)
I	43 ± 21	V_1	−4 ± 26
II	71 ± 28	V_2	52 ± 54
III	28 ± 28	V_3	98 ± 59
aVR	−57 ± 21	V_4	112 ± 53
aVL	8 ± 20	V_5	96 ± 39
aVF	49 ± 26	V_6	67 ± 25

ing complicated MI with ΣDE. A value <0.05 was considered significant. Data are expressed as mean ± SD.

RESULTS

Similarities in QRST time-integral values of 12-lead electrocardiograms during the two activation sequences: The QRST values of 12-lead ECGs during supraventricular drive were highly correlated with values during simulated left BBB (r = 0.88; p <0.001) (Figure 1). The correlation coefficients of ΣDE for the 2 activation sequences were highly significant (r = 0.95; p <0.001) (Figure 2). A paired *t* test revealed small but significant changes (p <0.05) in QRST values in leads II, III, aVR and aVF between the 2 activation sequences in patients without a prior anterior wall MI (Table I), and in leads I, II, III, aVR, aVF and V_1 in those with a prior MI and in all patients combined (Tables II and III). QRST values in leads I, II, III and aVF were greater during simulated left BBB than during sinus rhythm. However, there were no significant differences in QRST values in left precordial leads between the 2 activation sequences. The normal ranges used in this study are listed in Table IV.

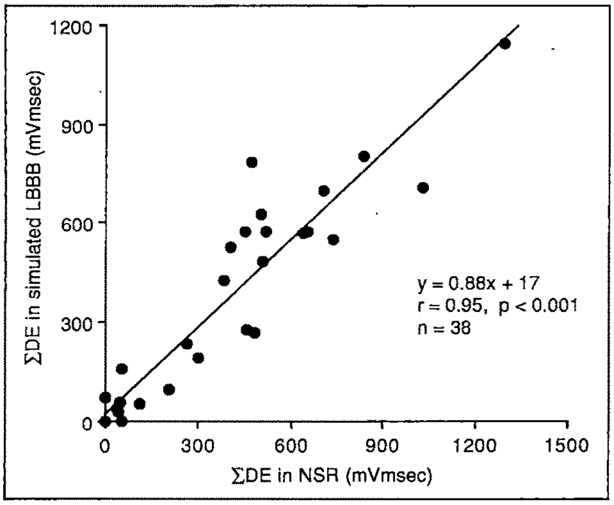

FIGURE 2. Correlation between ΣDE values during normal sinus rhythm (NSR, supraventricular complex) and simulated left bundle branch block (LBBB).

Standard 12-lead ECGs and QRST values of a representative case without MI during the 2 activation sequences are shown in Figure 3. QRST values were similar during simulated left BBB and sinus rhythm, but the QRST configurations of the 2 activation sequences were different. Although precordial leads showed QS patterns in V_1 and V_2 during simulated left BBB, QRST values remained within the normal range.

QRST time-integral values of prior anterior wall myocardial infarction during the two activation sequences: Standard 12-lead ECGs and QRST values during the 2 activation sequences of a representative case are shown in Figure 4. QRST values were similar during simulated left BBB and sinus rhythm (Figure 4), but the QRST configurations were different. Coronary arteriography showed a significant narrowing in the proximal segment of the left anterior descending artery. Left ventriculography revealed asynergy in anterolateral and apical segments; ejection fraction and asynergy index were 42% and 9, respectively. QRST values in leads I, V_3, V_4, V_5 and V_6 were less than the normal range in both activation sequences. The ΣDE was 676.2 mV · ms during simulated left BBB.

Diagnostic ability of QRST time-integral values to detect prior anterior wall myocardial infarction during simulated left bundle branch block: A criterion of $\Sigma DE \geq 40$ mV · ms for detection of an anterior wall MI was selected on the basis of statistical analysis. This diagnostic criterion showed a sensitivity of 88%, a specificity of 93%, and a diagnostic accuracy of 89%.

Relation of QRST time-integral values to severity of left ventricular wall motion abnormalities due to anterior wall myocardial infarction during simulated left bundle branch block: The ΣDE parameter derived from QRST values was significantly correlated with the ejection fraction and asynergy index during simulated left BBB ($p < 0.01$). The correlation between ΣDE and asynergy index was greater ($r = 0.79$; $p < 0.001$) (Figure 5) than that between ΣDE and ejection fraction.

DISCUSSION

The results show the following: (1) There was a significant correlation between QRST values of 12-lead ECGs during the 2 activation sequences in patients with and without a prior anterior wall MI. (2) Although QRST values in leads I, II, III, aVR, aVF and V_1 showed small but significant changes during simulated left BBB, there were no significant changes in QRST values in left precordial leads. (3) The ΣDE derived from QRST values of 12-lead ECGs in patients with a prior anterior wall MI during simulated left BBB and supraventricular drive were very similar. (4) The correlation between the asynergy index and ΣDE during simulated left BBB was highly significant. These findings

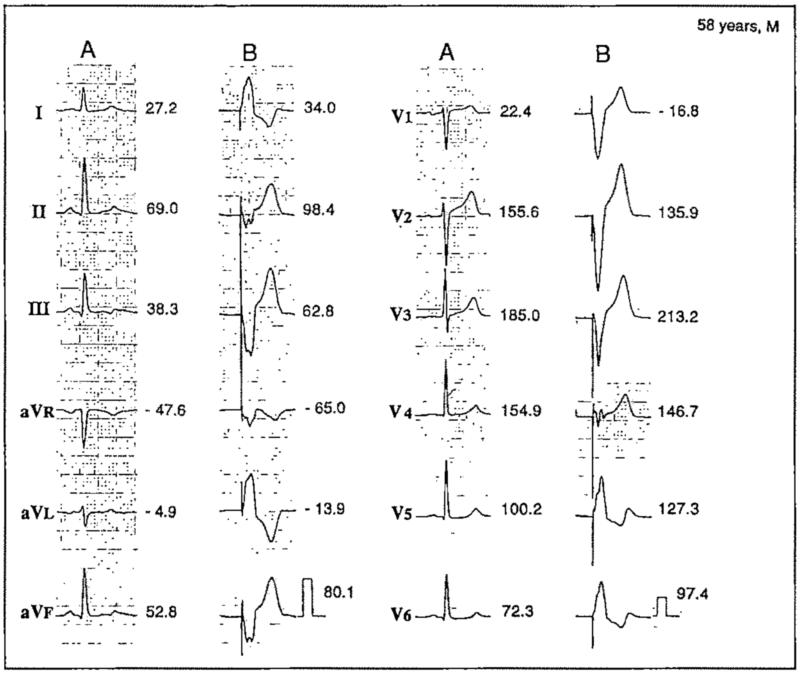

FIGURE 3. Twelve-lead electrocardiograms and QRST values during normal sinus rhythm *(A)* and simulated left bundle branch block *(B)* in representative patient without prior myocardial infarction.

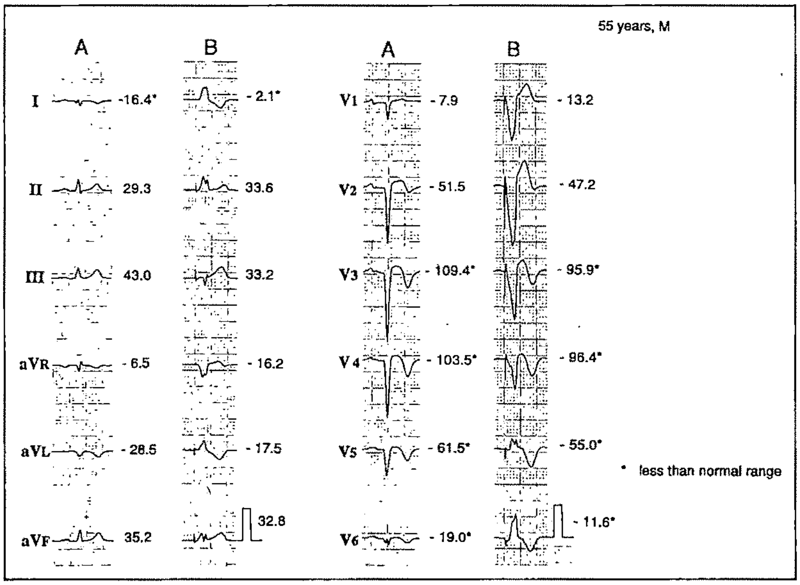

FIGURE 4. Twelve-lead electrocardiograms and QRST values during normal sinus rhythm *(A)* and simulated left bundle branch block *(B)* in representative patient with prior anterior wall myocardial infarction.

demonstrate that QRST values in each lead (especially left precordial leads) of 12-lead ECGs were similar during different activation sequences in the same patient, irrespective of the presence of a prior anterior wall MI. The QRST values in 12-lead ECGs may provide clinically useful information on the severity of left ventricular wall motion abnormalities complicated by prior anterior wall MI in the setting of left BBB.

The diagnosis of prior MI complicated by left BBB with the standard 12-lead ECGs is difficult.[1,2] Various electrocardiographic criteria have been proposed to improve the diagnosis of MI in the presence of left BBB; however, these criteria have been shown to be relatively insensitive and nonspecific for identifying the location of the MI.[1-4]

Wilson et al[5] introduced the concept of ventricular gradient, according to which QRST values calculated from data recorded by bipolar limb leads are largely independent of the activation sequence and dependent on repolarization properties. Abildskov et al[6] first demonstrated that this concept was applicable to QRST isointegral maps recorded by body surface unipolar leads with Wilson's central terminal. The usefulness of these maps for identifying and localizing ischemic or infarcted myocardium in the setting of left BBB has been investigated.[8,9] Hirai et al[8] recorded these maps in dogs during supraventricular drive and right atrial plus ventricular pacing after a left anterior descending coronary artery occlusion, and showed that there were only small differences during the 2 activation sequences in the maps recorded before and after the occlusion. The rationale for using these maps for the diagnosis of MI associated with an abnormal activation sequence is that the localized abnormalities of recovery properties caused by MI should be manifest in the maps independent of the activation sequence. Adachi et al[10] reported the applicability of this rationale to QRST values of 12-lead ECGs. It has been demonstrated that left ventricular wall motion abnormalities are associated with repolarization abnormalities.[19,20] Burgess et al[7] showed experimentally that QRST isointegral maps are closely related to the size and severity of thermally induced changes in recovery properties, and largely independent of changes in the activation sequence. However, there have been no reports concerning the usefulness of QRST values from 12-lead ECGs for detecting the severity and extent of repolarization abnormalities resulting from MI during abnormal activation. In the present study, we showed that QRST values from 12-lead ECGs are practical and useful for detecting the severity and extent of repolarization abnormalities due to MI, and that they reflect severity of left ventricular wall motion abnormalities due to MI during simulated left BBB.

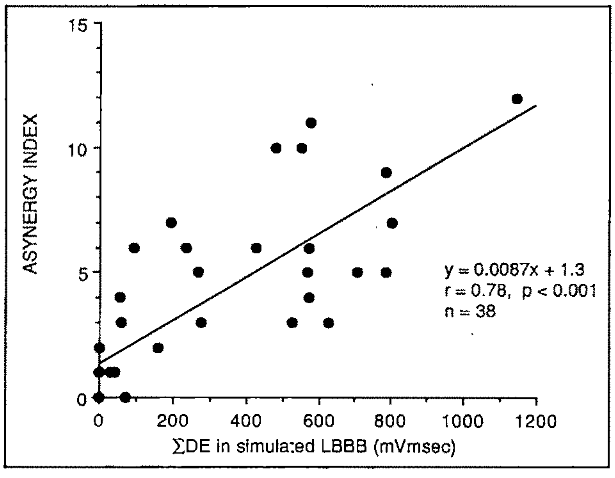

FIGURE 5. Scatterplot of ΣDE in simulated left bundle branch block (LBBB) plotted against asynergy index.

The QRST values of the 456 lead points (12 leads × 38 patients) were highly correlated between the 2 activation sequences. The correlation coefficient of ΣDE for the 2 activation sequences was highly significant. These findings demonstrate that the concept introduced by Wilson et al[5] is applicable to QRST values from 12-lead ECGs. However, Costard-Jäckle et al[12] reported that changes in the activation sequence gradually induced changes in repolarization properties in isolated rabbit hearts. Hanashima et al[13] showed that the cardiac surface QRST area changed according to the pacing site. Thus, these recent experimental studies emphasize that recovery properties or QRST values of the cardiac surface are not exclusively independent of the activation sequence. Changes in recovery properties due to an activation sequence have been partly attributed to electrotonic interaction, resulting in less disparity in repolarization.[12] We found that QRST values during the 2 activation sequences were very similar, although QRST values in inferior leads showed small but significant increases during simulated left BBB compared with during supraventricular complex. We paced the mid- to lower right ventricle to simulate left BBB; thus, our results are consistent with those of Abildskov et al, who reported that during right ventricular pacing, QRST values increased around the pacing site[21] and a vector of the ventricular gradient directed inferiorly in the frontal plane compared with atrial pacing in dogs.[22] To our knowledge, the present study is the first to demonstrate that the QRST values of 12-lead ECGs show small but significant changes in the inferior leads, but not in the left precordial leads, during right ventricular pacing in patients with and without a prior anterior wall MI.

Study limitations: There are some limitations of the present study. Right ventricular pacing was used to simulate left BBB. It is not precisely equivalent to the clinical conduction disturbance; however, the body surface ECGs obtained during right ventricular pacing in the present study showed changes in typical left BBB, including wide QRS duration, QS or rS patterns in the right precordial leads, and rsR′ patterns or monophasic R waves with notches or slurs in the left precordial leads. Vassallo et al[23,24] reported that right ventricular pacing may serve as a model of left BBB based on evidence from left ventricular endocardial mapping during right ventricular pacing. In the present study, we examined the effects of simulated left BBB on QRST values in patients with a prior anterior wall MI. Further study will be needed in patients with MI in other locations, such as the inferior wall.

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Electropharmacologic Effects and Pharmacokinetics of Almokalant, a New Class III Antiarrhythmic, in Patients with Healed or Healing Myocardial Infarcts and Complex Ventricular Arrhythmias

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The electropharmacologic effects and pharmacokinetics of almokalant, a new class III antiarrhythmic, were investigated in a randomized, placebo-controlled, double-blind study, and efficacy was evaluated. Ten post–myocardial infarction patients with complex ventricular arrhythmias were included and received, in randomized order on consecutive days, 4.5 mg (12.8 μmol) of almokalant or placebo intravenously over 10 minutes. One patient received infusion at a higher rate and developed self-terminating torsades de pointes. In the remaining 9 patients the corrected QT interval increased significantly: At the end of placebo infusion the corrected QT was 445 ± 18 ms and after almokalant 548 ± 53 ms ($p = 0.0015$). The signal-averaged electrocardiographic parameters did not change. The number of ventricular premature complexes decreased significantly during the first 15 minutes after almokalant infusion ($p = 0.04$). No additional proarrhythmic or other significant adverse events were noted. The almokalant plasma concentration showed a biphasic decrease with an elimination half-life of 2.4 ± 0.1 hours. Almokalant was rapidly cleared from the body with a clearance of 11 ± 1 ml/min/kg. When given with certain precautions almokalant appears safe and well-tolerated and may be antiarrhythmic by prolonging refractoriness.

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In animal experiments, the new class III antiarrhythmic almokalant ((4-[3-[ethyl[3-(propylsulfinyl) propyl] amino] - 2 - hydroxy-propoxy]-benzonitrile), H 234/09, Hässle, Sweden) prolongs the monophasic action potential and refractoriness of the atrium as well as the ventricle without affecting conduction velocity. In addition, it has positive inotropic effects, selectivity between cardiac and central nervous system effects, and is devoid of β-blocking properties. In studies on isolated human papillary muscle, almokalant has also had a selective action on cardiac repolarization and positive inotropic effects.[1] In this study the electropharmacologic effects and pharmacokinetics of a single infusion of almokalant were studied in post–myocardial infarction patients with complex ventricular arrhythmias. In addition, the efficacy in the suppression of ventricular arrhythmias was evaluated.

METHODS

Patients: Patients with a myocardial infarct older than 1 month, and having ≥720 ventricular premature complexes or ≥10 episodes of symptomatic nonsustained ventricular tachycardia on 24-hour Holter monitor were included in the study. Electrocardiographic exclusion criteria were sinus bradycardia (<50 beats/min) and second- or third-degree atrioventricular block. Patients with bundle branch block or symptomatic sinus node dysfunction were also excluded. Patients with a QT interval >520 ms and known proarrhythmic response with class Ia or III antiarrhythmic drugs were not allowed to participate. In addition, patients with angina pectoris, congestive heart failure class III and IV according to the criteria of the New York Heart Association, or other significant medical or mental conditions that would interfere with conduct or evaluation of the study were excluded. Before infusions, electrolyte disturbances, especially hypokalemia and hypomagnesemia, were ruled out. Therapy with β blockade and nifedipine was allowed; however, digitalis and other antiarrhythmic drugs had to be withdrawn for at least 5 half-lives. This study was approved by the institutional review board. Pharmacokinetic and biostatistical analyses were performed at Astra-Hässle Cardiovascular Research Laboratories.

Study design: The study was designed as a randomized, crossover, double-blind, placebo-controlled trial. After written informed consent, the patients were ad-

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TABLE I Baseline Characteristics

			Echocardiogram			24-Hour Holter			Signal-Averaged ECG			
Pt.	Age (yr) & Sex	LVEF (%)	LVESD (mm)	LVESD (mm)	LA (mm)	VPC	Runs	Frequency of Fastest Run (beats/min)	LP	QRS (ms)	D40 (ms)	V40 (μV)
1	54M	61	45	60	54	37,595	2	129	+	105	43	17
2	49M	45	37	59	43	6,213	7	106	+	115	37	17
3	66F	35	46	63	40	28,168	136	134	+	143	29	17
4	62M	42	49	65	39	833	1	101	+	108	38	18
5	38M	27	46	63	46	6,103	35	140	0	103	28	32
6	57M	57	35	54	34	17,788	20	125	+	103	36	17
7	65M	47	—	—	—	4,870	16	112	NE	—	—	—
8	65M	32	—	55	37	40,157	537	128	NE	—	—	—
9	62M	22	57	74	50	27,138	367	199	+	113	46	17
10	52M	28	51	66	36	8,425	58	158	0	95	20	71

ECG = electrocardiogram; LA = left atrial dimension long axis; LP = late potential; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; NE = not evaluable; Runs = number of nonsustained ventricular tachycardias during 24-hour Holter; VPC = number of ventricular premature complexes during 24-hour Holter; 0 = no late potential present; + = late potential present.

nitted to the coronary care unit and received 4.5 mg 12.8 μmol) of almokalant or placebo intravenously ver 10 minutes in randomized order on consecutive lays. The patients were in an overnight fasting condiion and stayed in bed before and until 3 hours after ach infusion. The effects were evaluated by 12-lead lectrocardiograms, signal-averaged electrocardiograhy,[2,3] continuous Holter monitoring, and blood samling for plasma concentration determination of the lrug. During each infusion, the 12-lead electrocardioram was continuously monitored. In addition, electroardiography, signal-averaged electrocardiography and lood sampling were performed before, at the end t = 0) and 5, 15, 30, 60, 90, 120 and 180 minutes after he end of infusion. Normal values for signal-averaged lectrocardiography were: QRS <114 ms, D40 <38 ms nd V40 >20 μV.[4] If 1 or more of these variables were bnormal, the signal-averaged electrocardiogram was onsidered abnormal.

Holter monitoring: Holter monitoring was perormed with the Marquette Laser System (Marquette lectronics, Milwaukee, Wisconsin) using modified eads V_1, V_5 and aVF. To evaluate the antiarrhythmic fficacy of almokalant, the number of ventricular preature complexes was determined for each 5-minute inerval during 30 minutes before and 30 minutes after ach infusion. The incidence of couplets and nonsusained ventricular tachycardia was too low during this eriod to be analyzed.

Evaluation of antiarrhythmic mechanism: To evalute the effect of action potential prolongation on spontaeous ventricular arrhythmias, the coupling interval of entricular premature complexes with identical morhology was measured before and at the end of each fusion. During each time period, ≥3 coupling inervals were measured and averaged. Patients with omplete suppression of ventricular arrhythmias, or in hom the morphology changed, were excluded from his analysis.

Pharmacokinetic analysis: The plasma samples ere analyzed for almokalant by a reversed phasequid chromatography. Maximal plasma concentration (C_{max}) was taken as the observed plasma concentration at the end of drug infusion. The equation of a 2 compartment model was fitted to the individual plasma concentrations by least-squares nonlinear regression.[5] The area under the plasma concentration versus time curve (AUC) was calculated by integration of the computer-derived equation:

$$\mathrm{AUC} = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$$

where the C_n and the λ_n are the intercepts and rate constants of the equation fitted to the plasma data. Total plasma clearance (CL) was calculated as: CL = dose/AUC. The volume of distribution at steady state (V_{ss}), and the volume at distribution equilibrium (V_z) were determined by the following equations, where AUMC is the area under the first moment versus time curve:

$$V_{ss} = \frac{\mathrm{AUMC} - \mathrm{Dose}}{[\mathrm{AUC}]^2} \quad \text{and} \quad V_z = \frac{\mathrm{Dose}}{\mathrm{AUC} \cdot \lambda_2}$$

The half-lives of the different phases of the plasma concentration versus time curve ($t_{1/2}$), were calculated from: $t_{1/2} = 0.693/\lambda_n$, where λ_n is the rate constant of the separate phases determined by log-linear regression of the declining plasma levels.

Statistical analysis: Effect was defined as the absolute measurement at the end of almokalant and placebo infusion of the electrocardiographic and signal-averaged electrocardiographic parameters. The number of ventricular premature complexes was analyzed before and after the end of each infusion. Carryover effects were studied by Student's *t* test. Period effects and direct-treatment effects were analyzed with use of Student's *t* test expressed as 95% confidence intervals. For asymmetric-distributed data, we used the Wilcoxon's rank-sum test. A p value <0.05 was defined as significant. All data are expressed as mean ± 1 SD. The maximal corrected QT[6] prolongation was calculated with the Lineweaver-Burk equation. To analyze the concentration-effect relation, we used the percentage of the

TABLE II Data of the Electrocardiogram and the Signal-Averaged Electrocardiogram

	Before	0	5	15	30	60	90	120	180
Data of the Electrocardiogram Before and After Placebo or Almokalant									
Placebo (10)									
HR (beats/min)	62 ± 6	62 ± 7	64 ± 7	64 ± 9	62 ± 6	61 ± 6	61 ± 8	63 ± 9	60 ± 4
PR (ms)	161 ± 24	157 ± 26	153 ± 25	156 ± 25	158 ± 30	157 ± 30	153 ± 30	152 ± 27	150 ± 23
QRS (ms)	106 ± 8	108 ± 8	105 ± 12	104 ± 8	106 ± 6	105 ± 8	105 ± 10	106 ± 9	108 ± 9
QT (ms)	441 ± 25	439 ± 15	432 ± 19	436 ± 32	444 ± 30	442 ± 32	442 ± 39	438 ± 18	444 ± 26
QTc (ms)	447 ± 21	445 ± 18	446 ± 21	448 ± 32	449 ± 34	443 ± 33	446 ± 34	446 ± 32	443 ± 32
Almokalant (10)									
HR (beats/min)	63 ± 5	59 ± 9	58 ± 6	58 ± 6	58 ± 7	56 ± 4	57 ± 7	59 ± 5	63 ± 6
PR (ms)	155 ± 26	159 ± 27	158 ± 25	159 ± 30	156 ± 26	156 ± 25	153 ± 26	152 ± 28	153 ± 25
QRS (ms)	105 ± 9	107 ± 8	108 ± 11	108 ± 9	107 ± 7	108 ± 10	107 ± 9	106 ± 10	106 ± 10
QT (ms)	440 ± 34	560 ± 75*	530 ± 67*	500 ± 46*	499 ± 59*	477 ± 42*	472 ± 41*	466 ± 29*	451 ± 31
QTc (ms)	450 ± 31	548 ± 53*	517 ± 55*	489 ± 48*	490 ± 63*	462 ± 38*	457 ± 34*	462 ± 30*	460 ± 30
Data of the Signal-Averaged Electrocardiogram Before and After Placebo or Almokalant									
Placebo									
QRS (ms)	113 ± 15 (6)	111 ± 17 (6)	112 ± 15 (7)	109 ± 14 (7)	112 ± 15 (7)	111 ± 14 (7)	115 ± 14 (6)	113 ± 15 (6)	111 ± 13 (7)
D40 (ms)	32 ± 11 (6)	31 ± 11 (6)	37 ± 13 (7)	32 ± 13 (7)	33 ± 15 (7)	33 ± 12 (7)	36 ± 7 (6)	32 ± 5 (6)	31 ± 11 (7)
V40 (μV)	31 ± 25 (6)	31 ± 27 (6)	28 ± 25 (7)	28 ± 23 (7)	29 ± 23 (7)	28 ± 25 (7)	20 ± 7 (6)	20 ± 6 (6)	29 ± 27 (7)
Almokalant									
QRS (ms)	112 ± 15 (7)	117 ± 19 (6)	113 ± 17 (6)	111 ± 16 (7)	111 ± 18 (6)	113 ± 19 (7)	106 ± 9 (6)	113 ± 15 (6)	112 ± 16 (7)
D40 (ms)	33 ± 8 (7)	36 ± 12 (6)	31 ± 11 (6)	31 ± 11 (7)	30 ± 10 (7)	30 ± 8 (7)	32 ± 14 (5)	30 ± 12 (6)	32 ± 8 (7)
V40 (μV)	29 ± 19 (7)	29 ± 19 (6)	30 ± 22 (6)	29 ± 21 (7)	29 ± 20 (6)	28 ± 18 (7)	29 ± 21 (6)	29 ± 25 (6)	27 ± 18 (7)

*$p < 0.05$.
All data are mean ± 1 SD.
Numbers in parentheses are the numbers of available patients.
Before = before infusion; 0 = end infusion (thereafter, 5, 15, 30, 60, 90, 120 and 180 minutes after the end of the infusion); HR = heart rate.

maximal effect as the dependent variable and the logarithm of the plasma concentration as the independent variable in a linear regression model.

RESULTS

Baseline characteristics: Table I lists the baseline characteristics of the 10 patients. Six patients had a healed inferior myocardial infarct, 1 patient had an inferoanterior infarct, 1 patient had an inferoposterior, and 2 patients an anterior infarct. No patient had symptoms or signs of heart failure. Only 2 patients received concomitant β blockade and 2 an angiotensin-converting enzyme inhibitor. The first patient was excluded from the analysis because of a proarrhythmic response after an infusion at too high a rate.

Electrocardiographic results: During and after infusion of almokalant no significant changes in heart rate, PR interval and QRS duration were noted compared with placebo (Table II). However, the QT interval was significantly prolonged (Figure 1). At the end of the placebo infusion the corrected QT was 445 ± 18 versus 548 ± 53 ms at the end of almokalant infusion (confidence interval 1.15–1.40; $p = 0.0015$). The maximal observed effect occurred at the end of the almokalant infusion and the interval was significantly prolonged until 120 minutes after the end of infusion. No changes in the signal-averaged electrocardiographic parameters occurred (Table II).

The effect on the coupling interval between sinus beat and ventricular premature complex was evaluable in 6 patients. It remained unchanged after placebo infusion (605 ± 78 ms before and 607 ± 70 ms at the end of infusion). In contrast, almokalant prolonged the coupling interval significantly from 592 ± 66 ms before infusion to 719 ± 74 ms at the end of infusion (confidence interval 44–180; $p = 0.008$) (Figure 2).

Antiarrhythmic efficacy: Antiarrhythmic evaluation of almokalant with respect to suppression of ventricular premature complexes was possible within the limited period of 30 minutes because the number of ventricular premature complexes was high and constant in almost all patients. Compared with placebo, almokalant significantly suppressed isolated ventricular premature complexes until 15 minutes after the end of infusion ($p = 0.04$) (Figure 3). None of the 9 evaluated patients had a proarrhythmic response.[7,8]

Pharmacokinetic results: The almokalant plasma concentrations at the end of infusion showed a wide range, from 216 to 690 nmol/liter (mean C_{max} 390 ± 157 nmol/liter) (Table III, Figure 4). The pharmacokinetics were best described by the equation of a 2-compartment model. There was a very rapid distribution to extravascular tissues, which accounted for the large interindividual differences in the C_{max} and in the central volumes of distribution. However, the difference between individual plasma levels during the elimination phase was small and a half-life of 2.4 ± 0.1 hours was observed. The volume of distribution at steady state and at equilibrium were similar. The total plasma clearance of 11 ± 1 ml/min/kg indicates that almokalant was rapidly cleared from the body. The 5 patients with ejection fractions $\leq 35\%$ had a maximal plasma concentration of 457 ± 160 nmol/liter, whereas this value in the 4 patients with ejection fractions $>35\%$ was 258 ± 54

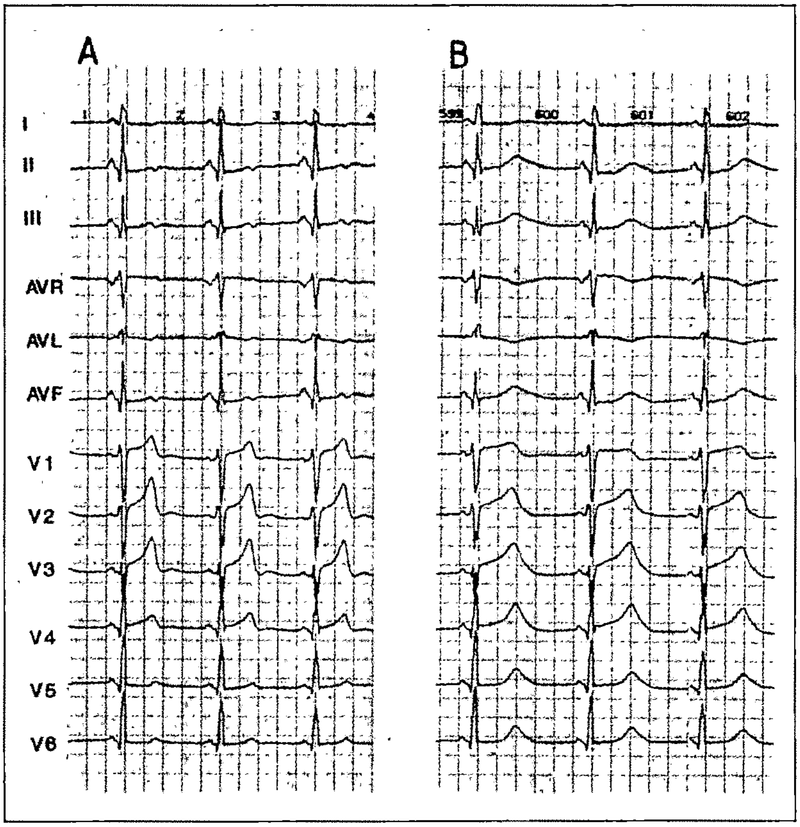

FIGURE 1. Observed changes of the QT interval and the morphology of the ST-U segment after almokalant infusion in patient 10. Similar changes were seen in all other patients. Note the prolongation of the QT interval accompanied by flattening of the T wave. In addition, the U wave became more pronounced or incorporated in the TU complex. (1 cm = 1 mV, paper-speed 1 cm = 400 ms.) *A*, electrocardiogram before almokalant infusion; *B*, electrocardiogram at the end of almokalant infusion.

TABLE III Pharmacokinetic Data of Almokalant

Maximal plasma concentration	390 ± 157 nmol/liter
Distribution half-life	1.9 ± 0.2 minutes
Elimination half-life	2.4 ± 0.1 hour
Area under the plasma concentration versus time curve	244 ± 30 nmol/liters · hour
Central volume of distribution	0.16 ± 0.07 liters/kg
Volume at distribution equilibrium	2.3 ± 0.3 liters/kg
Volume of distribution at steady state	1.8 ± 0.4 liters/kg
Total plasma clearance	11.3 ± 1.4 ml/min/kg

nmol/liter. However, no statistically significant relation between these parameters was found.

Corrected QT interval and almokalant plasma concentration were both maximum at the end of infusion and decreased thereafter without any sign of a hysteresis effect. The relation between these parameters could be best described by: percentage maximal prolongation of corrected QT interval = −139 + (105 · log plasma concentration). Interpolating the regression line showed a value of log (A50) = 1.8, so that A50 = 63.1 nmol/

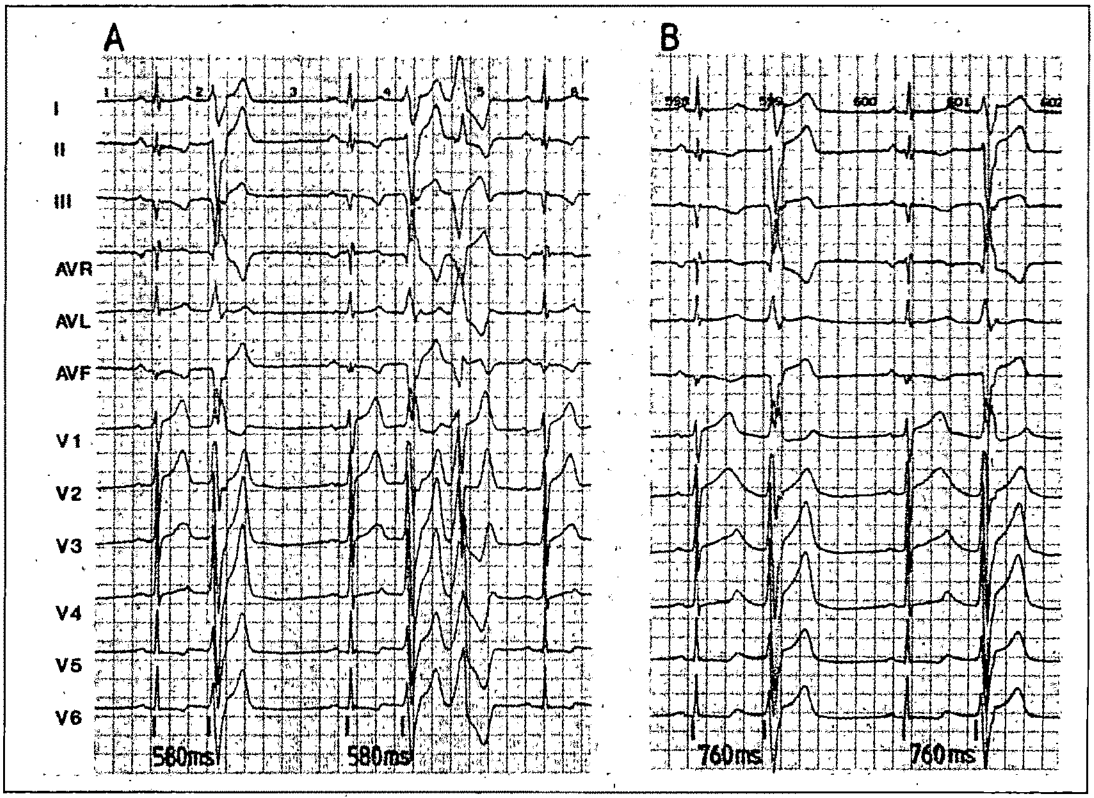

FIGURE 2. The coupling interval of a premature ventricular complex in a patient before *(A)* and at the end *(B)* of almokalant infusion (1 cm = 1 mV, paperspeed 1 cm = 400 ms).

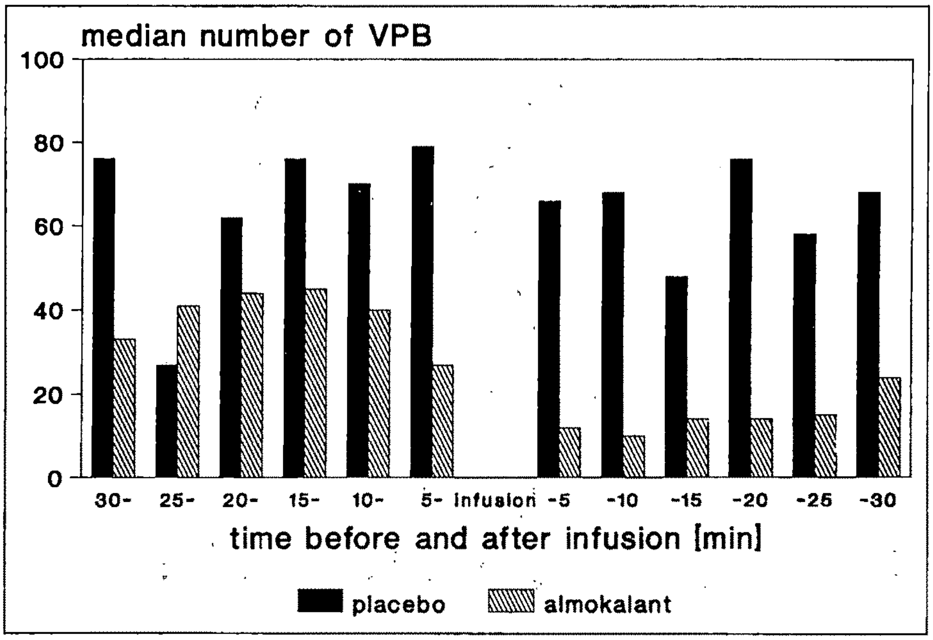

FIGURE 3. Antiarrhythmic effects of almokalant in all patients. Median number of ventricular premature beats (VPB) with 5-minute intervals during 30 minutes before and after placebo and almokalant infusion.

liter. A50 represents the plasma concentration at 50% of the maximal prolongation of the corrected QT interval (Figure 5).

Adverse events: The first patient had to be withdrawn because the rate of the almokalant infusion was too high. This patient experienced self-terminating episodes of torsades de pointes, from which he recovered uneventfully. Instead of 4.5 mg of almokalant in 10 minutes, 3 mg in 3 minutes were given. Also, hypomagnesemia was inadvertently present. No patient developed signs of left ventricular dysfunction or a decrease in blood pressure. One patient reported a transient metallic taste during almokalant infusion.

DISCUSSION

The main electrocardiographic effect of almokalant was a significant QT prolongation persisting at least 120 minutes after a single 10-minute infusion. The relatively low sinus rate[9] (preexisting and throughout the study) and the high plasma concentrations[10] may have contributed to the pronounced QT prolongation. Almokalant infusion was accompanied by evident changes of the morphology of the ST-U segment: a flattening of the T wave with increasing U wave. The absence of heart rate changes confirms animal data showing absence of β-blocking effects. In addition, the unchanged PR duration in this study suggests lack of effects on intraatrial or atrioventricular conduction. Finally, almokalant does not influence intraventricular conduction because QRS prolongation was not observed.

Previous studies have shown changes in the signal-averaged electrocardiogram during treatment with antiarrhythmic drugs, which depress conduction velocity.[11,12] To date the disappearance of a late potential has only been observed after antiarrhythmic surgery.[13-15] In animal experiments and in the present study, almokalant had no effects on conduction velocity and therefore no changes in the parameters of the signal-averaged electrocardiogram were found.

The prolongation of refractoriness after almokalant was accompanied by clear antiarrhythmic effects. It reduced the number of ventricular premature complexes

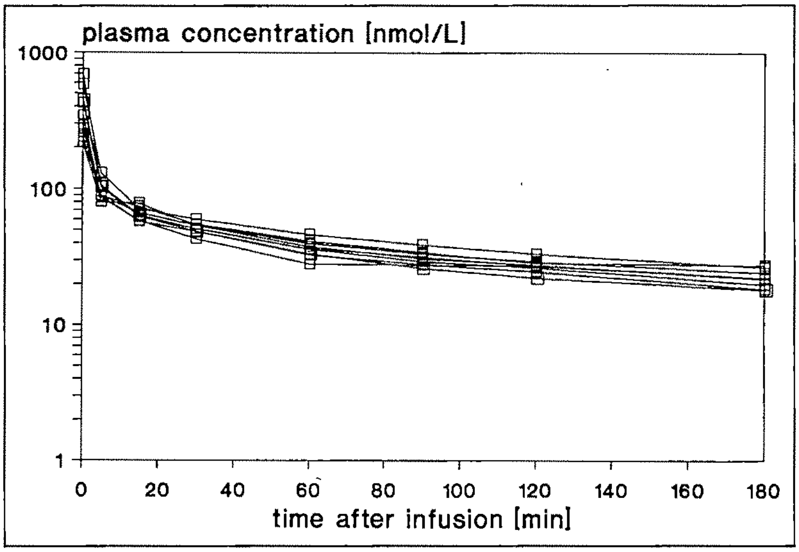

FIGURE 4. Plasma concentration of almokalant versus time after the infusion of all patients (*y axis* is log scale).

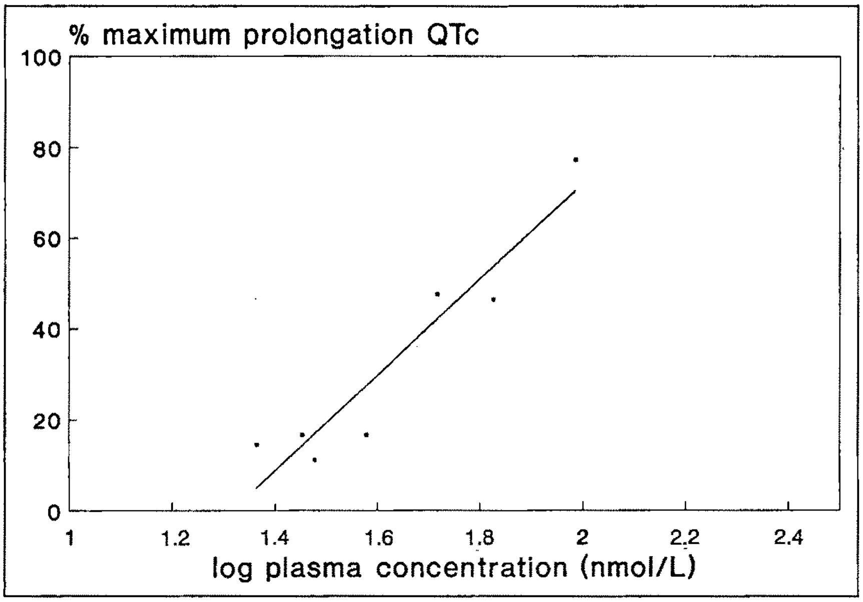

FIGURE 5. Relation between prolongation of the corrected QT interval and almokalant plasma concentration. Mean values at each time interval were used.

for a short time, but this was clinically and statistically significant. In general, the class III effect of an antiarrhythmic drug is not associated with suppression of premature complexes, but with prevention or termination of reentrant phenomena. One may speculate that if prolongation of refractoriness could influence the arrhythmia substrate, the result might be (1) a sudden disappearance of ventricular premature complexes, or (2) an increase in the coupling interval of the premature complex with or without eventual suppression of the arrhythmia. The sudden suppression of ventricular premature complexes during almokalant therapy in 2 patients may be compatible with arrhythmia due to reflection, reentry or abnormal automaticity. Theoretically, these arrhythmia mechanisms are not influenced by potassium channel blockade and their temporal coupling to the normal sinus beat would remain unchanged. As a consequence, extension of the refractory period in the normal myocardium precludes expression of these arrhythmia mechanisms because of exit block. In contrast, the other patients with incomplete suppression of ventricular arrhythmias had a significant increase of the coupling interval. This suggests an arrhythmia mechanism linked to the end of the action potential, resulting in longer coupling intervals of premature complex when the action potential is prolonged by almokalant. It is tempting to hypothesize triggered activity as arrhythmogenic mechanisms.

After infusion, almokalant was rapidly distributed and thereafter rapidly cleared from the body. The pharmacokinetic constants obtained in our patients were comparable to those observed in young healthy male subjects.[10] However, the plasma level at the end of infusion was higher and the elimination half-life was shorter in our study group. This was mainly due to the smaller volume of distribution, which may have resulted from depressed left ventricular function. However, the difference may also be due to the fact that the pharmacokinetic constants in the healthy subjects are derived from plasma concentrations up to 24 hours after drug administration.

Looking at the changes in the corrected QT intervals after the almokalant infusion, there was an evident concentration-effect relation. This suggests that the action potential–prolonging effects may be predictable in individual patients, thereby enhancing the clinical applicability of almokalant. Applicability would also include a predictable relation between QT prolongation and antiarrhythmic efficacy. However, a relation between degree of QT prolongation and antiarrhythmic efficacy has so far not been observed.[16-18]

With use of the normal infusion rate, no clinically significant adverse effects or proarrhythmic events occurred. Therefore, almokalant appears safe at the dose tested. In this respect one should note that in the present study, peak plasma concentrations were much higher than in healthy male subjects.[10] Such high concentrations may not be necessary to reach antiarrhythmic efficacy in clinical practice. Only the first patient, receiving infusion at too high a rate, had a proarrhythmic response. Recently, the hypothetical relation between almokalant infusion rate and induction of torsades de pointes was confirmed in animal studies (Carlsson et al, unpublished observations).

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Acute Hemodynamic and Electrophysiologic Effects and Safety of High-Dose Intravenous Diltiazem in Patients Receiving Metoprolol

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The anti-ischemic efficacy of diltiazem may improve with increments in dosage and with additional β-blocking therapy. However, the combined administration could lead to adverse effects through amplification of negative inotropic and chronotropic properties. To evaluate hemodynamic tolerability and safety of high-dose intravenous diltiazem in patients with coronary artery disease receiving long-term metoprolol treatment, 9 such patients were studied for 30 minutes after onset of intravenous diltiazem administration (0.5 mg/kg for 5 minutes, followed by 15 mg/hour). Diltiazem plasma levels peaked at 5 minutes (641 ± 74 μg/liter), decreasing to 177 μg/liter at 30 minutes. Average metoprolol levels (43 ± 12 μg/liter) did not change. Diltiazem immediately decreased systemic vascular resistance, left ventricular systolic and mean aortic pressures (29, 21 and 20%, respectively, at 5 minutes), and they remained significantly reduced at 30 minutes. Heart rate initially increased by 11% during the bolus infusion ($p < 0.05$). Concomitantly, contractility indexes V_{max} and Vce_{40}, measured at fixed heart rates, also increased significantly by 11%. Both heart rate and contractility indexes returned to baseline levels thereafter. Cardiac output increased by 10% (p = not significant), stroke index remained unchanged, but stroke work decreased significantly by 20%. Also, the tension-time index was significantly reduced (23%). Diltiazem induced moderate negative lusitropic effects, the first derivative of negative left ventricular pressure decline decreased by 12% and Tau$_2$ lengthened by 13%. Concomitantly, left ventricular filling pressure increased from 19 ± 2 to 23 ± 3 mm Hg, but only at 5 and 15 minutes. PQ, QRS and QTc intervals were not affected. Thus, high dosages of intravenous diltizem are hemodynamically well tolerated and preserve cardiac pump function in patients taking chronic β blockade. The predominant systemic vasodilating effects and subsequent reduction in myocardial oxygen demand and cardiac work are likely to magnify the anti-ischemic potential of diltiazem, already afforded by coronary flow improvement after high-dose administration.

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Calcium antagonists and β-blocking agents are independently well accepted as treatment for myocardial ischemia. In combination, several of their individual effects on the myocardial oxygen supply-demand ratio are complementary and therefore may result in an augmentation of overall anti-ischemic efficacy. Thus, diltiazem, through its systemic vasodilating properties, unloads the heart and thereby may increase the reduction in myocardial oxygen demand already achieved by the reduction in heart rate and, possibly, in contractility by metropolol. In addition, diltiazem may improve coronary flow. On the other hand, certain pharmacologic properties may be amplified, such as negative inotropic and chronotropic effects with subsequent adverse reactions when both compounds are combined. The occurrence of pharmacologic interactions, both desired and unwanted, depends largely on dosages and mode of administration. Intravenous diltiazem improves coronary flow only when relatively high dosages are administered,[1] whereas negative inotropic and chronotropic properties are also dose-related.[2] With oral administration the latter effects are less clear. In humans, combined medication of oral diltiazem and β-blocking agents is generally well tolerated and results in better anti-ischemic efficacy than diltiazem alone.[3,4]

In contrast, the acute hemodynamic profile, anti-ischemic efficacy and tolerability of intravenous diltiazem in patients taking long-term β-blocking therapy are less clear.[5,6] Relatively low dosages of diltiazem reduce heart rate, contractility and cardiac output and may give rise to untoward clinical events.[7] This may be different with high dosages of intravenous diltiazem. In untreated patients, a relatively high-dose intravenous administration of diltiazem does not affect sinus rate or may increase it,[1] in contrast to low-dose infusion.[8,9] Also, conduction disturbances do not occur.[9] Moreover, in untreated patients with diminished left ventricular function, high intravenous dosages improve cardiac pump function (unpublished observation). To evaluate whether such effects pertain in the presence of long-term β-blocking therapy, the present study investigated the acute hemodynamic and electrophysiologic profile and safety of high-dose intravenous diltiazem in such patients.

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TABLE I Individual Clinical and Angiographic Data

Pt.	Age (yr) & Sex	Daily Dose of Metoprolol (mg)	Previous MI	AP	LVEDV (ml/m^2)	LVEF (%)	Coronary Angiogram (% luminal narrowing)		
							LAD	LC	Right
1	48M	50	Inferior	–	84	69	0	0	70
2	41M	100	Lateral	++	76	57	100	50	0
3	66F	150	0	++	49	67	100	0	100
4	56M	100	Inferior	–	70	47	80	0	50
5	64M	100	Anterior	–	65	57	80	0	0
6	54M	100	Inferior	++	130	34	0	80	100
7	50F	100	Inferopost.	++	91	52	70	90	0
8	64M	100	0	++	94	60	0	0	90
9	69F	200	0	++	64	74	0	60	0
Mean ± SEM	75 ± 3	111 ± 14			80 ± 7.8	57 ± 12			

AP = exercise-induced angina pectoris; Inferopost. = inferoposterior; LAD = left anterior descending artery; LC = left circumflex; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MI = myocardial infarction; ++ = present; – = absent.

METHODS

Nine patients (6 men and 3 women, mean age 57 years [range 41 to 69]), were studied after approval of the study by the institutional ethical review board and after informed consent. Six patients had a documented myocardial infarction (1 anterior, 1 lateral and 4 inferior). Unstable angina, recent (<3 months) myocardial infarction, coronary angioplasty or bypass grafting, renal or hepatic dysfunction and insulin-dependent diabetes mellitus were exclusion criteria. Furthermore, all patients were normotensive, without conduction disturbances or heart failure. All patients received chronic oral metoprolol, 50 to 200 mg/day (average 111 ± 14 mg, mean ± SEM). The last dose of metoprolol was administered 4 to 12 hours before the investigation so that resting heart rates before the investigation were between 45 and 70 beats/min. Other cardiac therapy was discontinued 36 to 72 hours before the study. Only short-acting nitroglycerin was allowed until 4 hours before catheterization. To participate in the study, significant coronary artery disease, defined as a ≥50% luminal diameter stenosis in 1 or more epicardial coronary arteries, had to be present. Four patients had 1-vessel and 5 patients had 2-vessel disease. Overall left ventricular ejection fraction was within normal limits (57 ± 12%, range 34 to 74). Individual clinical and angiographic data are given in Table I.

Instrumentation: Studies were performed in the morning, after an overnight fast, without premedication. First, routine left and right arteriography with nonionic contrast medium (Iopamidol) were performed, using the Seldinger approach. Next, a 7Fr Cordis microtip manometer catheter was positioned in the left ventricle via a Desilet system in the right femoral artery, the side arm of which was used to record arterial pressures. A 7Fr Swan-Ganz thermodilution catheter was advanced from a femoral vein with its tip in a pulmonary artery and its proximal lumen in the right atrium to enable pulmonary arterial and right atrial pressure recordings and to measure cardiac output.

Measurements: Fluid-filled catheters were calibrated using a zero reference level set at midchest. The micromanometer pressures were balanced to zero and superimposed on the conventional pressure tracings. Left ventricular, aortic, pulmonary and right atrial pressures and the first derivative of left ventricular pressure (dP/dt) were recorded on paper in the appropriate pressure ranges at different paper speeds (e.g., 25, 100 and 250 mm/s) using a CGR 1000 Cath Lab System. Cardiac output was measured with the thermodilution method and recorded on paper at a speed of 10 mm/s. Moreover, it was determined on-line using a Mennen Cath Lab System Computer. With the same system, all pressures and pressure-derived indexes of contractility and relaxation (left ventricular peak dP/dt positive and negative, dP/dt/P at 40 mm Hg [Vce_{40}] and V_{max} total pressure)[10] were determined on-line and calculations made from 15 to 20 consecutive beats. In addition, isovolumetric relaxation parameters, Tau, Tau_1 and Tau_2, were determined off-line in a beat-to-beat program using a semilogarithmic model.[11] Throughout the study, leads I, II and V_5 were continuously monitored and recorded at a paper speed of 25 and 100 mm/s for the determination of heart rate and the measurement of PQ, QRS and QT intervals.

Calculations: From the measured variables, the following hemodynamic parameters were calculated: stroke volume index (ml/beat/m^2) as cardiac index (liters/min/m^2) divided by heart rate (beats/min) × 1,000; stroke work index (g · m/m^2) as stroke volume index × (mean arterial pressure minus left ventricular end-diastolic pressure [mm Hg]) × 0.0136; systemic vascular resistance (dynes s cm^{-5}) as (mean arterial pressure [mm Hg] minus mean right atrial pressure [mm Hg]) × 80 divided by cardiac output (liters/min); pulmonary vascular resistance (dynes s cm^{-5}) as (mean pulmonary artery pressure [mm Hg] minus left ventricular mean diastolic pressure [mm Hg]) × 80 divided by cardiac output; the tension time index (mm Hg/min) as product of left ventricular systolic pressure (mm Hg) and heart rate divided by 1,000.

Study protocol: After a stabilization period of 20 minutes after instrumentation, approximately 40 minutes after coronary angiography, multiple control measurements of all hemodynamic parameters were made to obtain stable baseline values. Then, diltiazem, 0.5 mg/kg body weight, was administered intravenously over 5 minutes, followed by a continuous infusion of 15 mg/hour. Hemodynamic and electrocardiographic variables were redetermined at 1, 3, 5, 10, 15, 20 and 30 minutes after onset of diltiazem administration. Hemodynamic measurements were performed at basal and fixed atrial pacing rates, 15 beats above basal rates. Cardiac output was determined at baseline and at 5, 10, 20 and 30 minutes after onset of infusion. Only values that varied within 5% were accepted. Plasma levels of diltiazem were determined at baseline and at 5, 10, 15, 20 and 30 minutes after onset of drug administration.

Statistical analysis: An analysis of variance for repeated measurements was used, followed by the Dunnett procedure for comparing all means with control. A 2-tailed p value <0.05 was considered to indicate a significant difference from baseline values. All values are given as mean values ± SEM.

RESULTS

Diltiazem plasma levels: Changes in diltiazem plasma levels are presented in Figure 1. Maximal levels (641 ± 74 μg/liter) were reached at 5 minutes after onset of diltiazem administration, gradually decreasing thereafter. At the end of the study, plasma diltiazem levels were still in the therapeutic range (177 ± 14 μg/liter). Mean metoprolol levels were 43 ± 12 μg/liter at baseline and did not change during diltiazem infusion.

Hemodynamic changes during diltiazem infusion (Table II): Diltiazem immediately decreased left ventricular systolic and mean aortic pressures, with a significant reduction after 3 minutes (Figure 2); maximal reductions of 21 and 20%, respectively, were observed at the end of the bolus infusion. Pressures remained at this level throughout the study. Concomitantly, systemic vascular resistance decreased from 1,868 ± 169 (control) to 1,352 ± 175 dynes s cm^{-5} at 5 minutes, a reduction of 29% ($p < 0.05$). Although systemic resistance tended to increase during maintenance infusion, it remained significantly reduced during the entire study. Heart rate initially increased at 3 and 5 minutes by 11%, from 61 ± 3 beats/min (control) to 67 ± 3 beats/min (5 minutes), but returned to baseline values thereafter. Similar to changes in heart rate, cardiac output increased by 10% at the end of the infusion period (p = not significant compared with control, Figure 3). Stroke index did not change. However, stroke work index decreased significantly throughout the study, by 20% at 5 minutes and 15% at 30 minutes. Also, the tension-time index, an index of myocardial oxygen demand, was significantly reduced throughout the study, with maximal changes of 23% at 10 and 15 minutes, respectively. Changes in contractility indexes were variable (Figure 4). A persistent, significant 11% decrease in left ventricular peak dP/dt positive was observed, starting from 10 minutes. In contrast, the velocity parameters Vce_{40} and V_{max} increased significantly during the bolus infusion period, but thereafter remained unchanged compared with baseline values. The peak negative value of LV dP/dt was reduced by 12% throughout the study period. In addition, of the isovolumetric indexes, Tau_2 lengthened significantly by 13% (Figure 4), whereas Tau and Tau_1 tended to increase. Left ventricular end-diastolic and mean pulmonary artery pressures increased, although moderately. Left ventricular filling pressure increased from 19 ± 2 mm Hg at baseline to 23 ± 3 mm Hg at 5 and 15 minutes, respectively (p = 0.05), accompanied by similar moderate elevations in mean pulmonary artery pressure. Also, right atrial pressure tended to increase, although changes here were not significant. Pulmonary vascular resistance was unaffected by diltiazem.

Electrophysiologic effects: Electrocardiographic parameters are given in Table III. Although PQ time prolonged slightly after diltiazem administration (baseline 177 ± 11 to 184 ± 12 at 20 minutes), this effect was not significant. Also, QRS, QT and QTc intervals remained unaltered. Premature ventricular extrasystoles were present in patient 6 from the start of the study until the end; however, they did not change in frequency or severity during diltiazem administration.

Adverse effects: No adverse effects were observed during the study.

DISCUSSION

The additional clinical benefit achieved by combined administration of oral diltiazem and beta-adrenergic blockade has been well established.[3,4] Besides an improvement in clinical well-being, the objective benefits include an increase in exercise duration and time to development of ischemic electrocardiographic changes during stress testing. In otherwise untreated patients, intravenous diltiazem also induces a clear anti-ischemic effect, at least when relatively high dosages are administered, such as in the present study.[1] In contrast, conflicting results are reported with regard to anti-ischemic efficacy when lower dosages, i.e., 18 to 35 μg/kg, are administered.[5,12–14] At high dosages, diltiazem decreases afterload without apparent changes in heart rate and contractility and subsequently diminishes myocardial oxygen demand.[1] Also, at high, but not at low dosages, a significant improvement in coronary flow is observed.[1,5,13–17] Moreover, relatively high dosages are

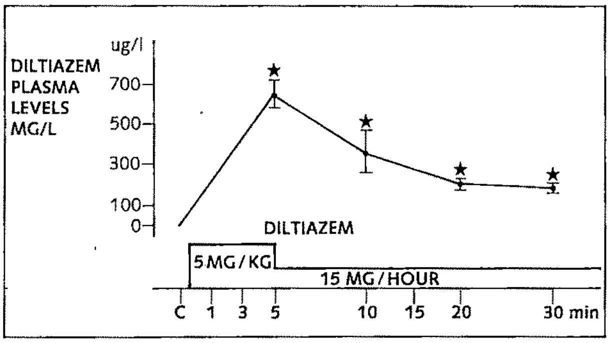

FIGURE 1. Plasma diltiazem levels after administration of 0.5 mg/kg over 5 minutes, followed by a maintenance infusion of 15 mg/hour. Maximal plasma levels of diltiazem were reached after 5 minutes (641 ± 74 μg/liter). At the end of the infusion, plasma levels were still in the therapeutic range (177 ± 14 μg/liter).

TABLE II Systemic Hemodynamic Changes During Diltiazem Administration

		Time After Onset of Diltiazem Infusion (0.5 mg/kg^{-1} for 5 minutes, followed by 15 mg/hour)						
		Minutes						
Hemodynamic Variables	Baseline	1	3	5	10	15	20	30
Heart rate (beats/min)	61 ± 3	64 ± 3	67 ± 3*	67 ± 3*	57 ± 2	57 ± 3	58 ± 3	57 ± 3
Tension time index (mm Hg/min)	9.5 ± 0.6	10.1 ± 0.7	8.4 ± 0.4	8.2 ± 0.3*	7.3 ± 0.3*	7.3 ± 0.4*	7.7 ± 0.4*	7.6 ± 0.4*
Left ventricular systolic pressure (mm Hg)	157 ± 9	159 ± 11	126 ± 5*	123 ± 5*	128 ± 5*	129 ± 6*	133 ± 6*	134 ± 7*
Left ventricular end-diastolic pressure (mm Hg)	19 ± 2	19 ± 3	20 ± 2	23 ± 3*	22 ± 2	23 ± 2*	22 ± 2*	22 ± 3
Mean arterial pressure (mm Hg)	117 ± 6	123 ± 8	100 ± 3*	94 ± 4*	100 ± 3*	101 ± 4*	103 ± 5*	102 ± 4*
Cardiac index (liters/min/m^2)	2.61 ± 0.15	—	—	2.86 ± 0.18	2.67 ± 0.19	2.55 ± 0.17	2.50 ± 0.17	2.53 ± 0.12
Right atrial pressure (mm Hg)	8 ± 1	—	—	9 ± 2	12 ± 2	11 ± 2	11 ± 2	11 ± 2
Systemic vascular resistance (dynes s cm^{-5})	1,868 ± 169	—	—	1,352 ± 175*	1,508 ± 157*	1,597 ± 156*	1,672 ± 197*	1,587 ± 113*
Stroke index (ml/beat/m^2)	43 ± 3	—	—	43 ± 2	47 ± 3	45 ± 2	43 ± 3	45 ± 2
Stroke work index (g · m/m^2)	58 ± 4	—	—	41 ± 3*	49 ± 5*	47 ± 4*	47 ± 5*	49 ± 4*
LV dP/dt positive (mm Hg · s^{-1})†	1,467 ± 69	1,480 ± 72	1,454 ± 74	1,347 ± 56	1,399 ± 94*	1,311 ± 79*	1,313 ± 63*	1,328 ± 74*
Vce_{40} (s^{-1})†	27 ± 1	27 ± 1	29 ± 1*	28 ± 1	27 ± 1	26 ± 1	26 ± 1	26 ± 1
V_{max} (s^{-1})†	39 ± 1	39 ± 1	46 ± 2*	44 ± 2*	42 ± 2	40 ± 1	40 ± 1	40 ± 1
LV dP/dt negative (mm Hg · s^{-1})†	1,698 ± 125	1,732 ± 126	1,498 ± 90*	1,400 ± 87*	1,486 ± 111*	1,391 ± 89*	1,560 ± 137*	1,549 ± 130*
Tau_2 (ms)†	48 ± 3	47 ± 3	53 ± 3	56 ± 4	55 ± 4	55 ± 4*	55 ± 4*	53 ± 5
Mean pulmonary artery pressure (mm Hg)	21 ± 2	21 ± 2	22 ± 2	24 ± 2*	23 ± 2	23 ± 2*	23 ± 2	22 ± 2
Pulmonary vascular resistance (dynes s cm^{-5})	128 ± 21	—	—	128 ± 22	128 ± 17	147 ± 24	144 ± 26	138 ± 21

*$p < 0.05$.
†Variables measured at fixed pacing rate.
Values are mean ± SEM.
dP/dt = first derivative of left ventricular pressure; LV = left ventricular; Tau = time constant of left ventricular/isovolumic relaxation[10]; Vce_{40} and V_{max} = left ventricular/isovolumic velocity of contraction indexes.[10]

well tolerated, at least in patients who are not taking concomitant β blockade (unpublished observation).

The present study indicates that in patients with normal ventricular function taking chronic β-blocking therapy, high dosages of intravenous diltiazem have no negative effects on cardiac pump function. Moreover, they do not result in negative chronotropic properties or conduction disturbances. In contrast, a sustained systemic vasodilating effect occurs, accompanied by a significant, but well-tolerated reduction in left ventricular systolic and aortic pressures. Despite a temporary 10% increase in heart rate, the net result is a significant and persistent decrease in the rate-pressure product and in myocardial oxygen demand. Simultaneously, cardiac work diminishes considerably. These observations indicate that in patients receiving long-term β-blocking therapy, high-dose intravenous diltiazem is hemodynamically well tolerated and results in potential anti-ischemic effects, (i.e., a reduction in myocardial oxygen demand). Since coronary flow also improves with high-, but not with low-dose intravenous diltiazem, a drug regimen as applied in the present study may be useful during acute ischemic episodes. Obviously, the acute hemodynamic effects of high-dose intravenous diltiazem do not necessarily reflect hemodynamic changes during long-term oral administration.

Inotropic and lusitropic effects of high-dose diltiazem and chronic beta blockade: The moderate increase in left ventricular filling pressure suggests a negative inotropic effect of diltiazem in the present condition,

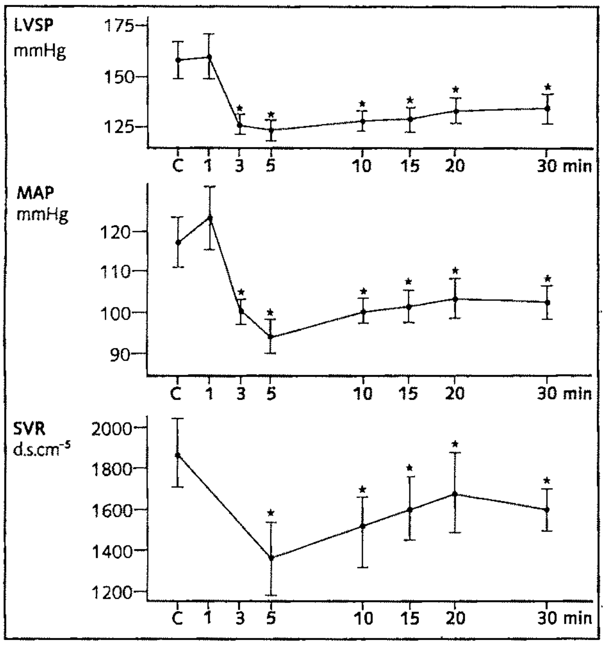

FIGURE 2. Acute but persisting systemic vasodilating effects of diltiazem. At the end of the bolus infusion, after 5 minutes, systemic vascular resistance (SVR) had decreased by 29%, accompanied by 21 and 20% reductions in left ventricular systolic (LVSP) and mean aortic (MAP) pressures, respectively. Changes were still significant at the end of the infusion. C = control.

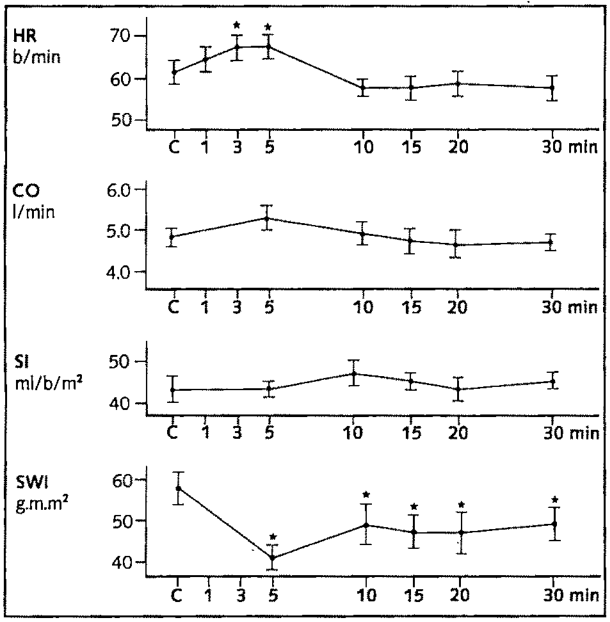

FIGURE 3. Heart rate (HR) initially increased during the bolus infusion by 11%, but returned to baseline levels thereafter. Cardiac output (CO) tended to increase (10%, p = not significant), but stroke index (SI) did not change. In contrast, a significant, persisting reduction in stroke work index (SWI) occurred. C = control.

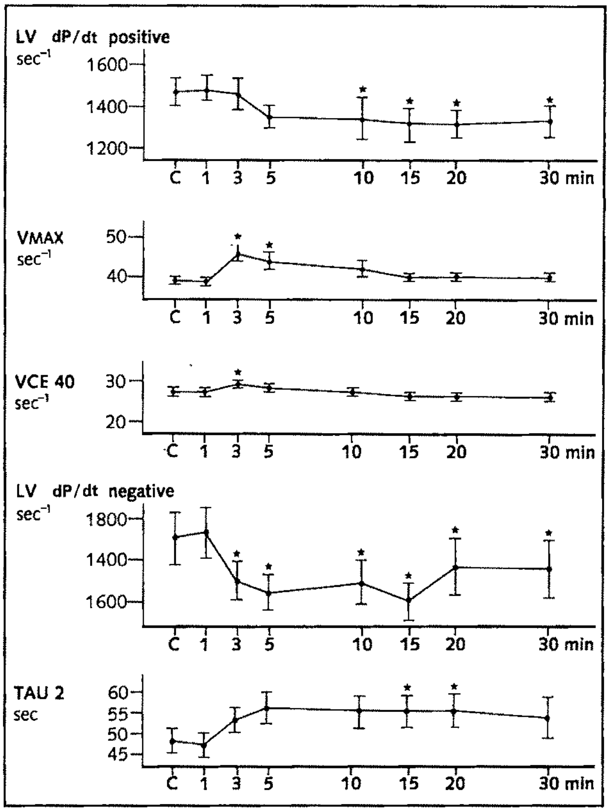

FIGURE 4. Inotropic and lusitropic effects of high-dose diltiazem in the presence of metoprolol, measured at fixed pacing heart rates. Isovolumetric contractility indexes VMAX and VCE 40 initially increased by 11% during the bolus infusion, but returned to baseline levels thereafter. In contrast, the first derivative of positive left ventricular pressure (LV dP/dt) decreased during the later phase of the study, possibly reflecting the concomitant reduction in afterload. Similarly, LV dP/dt negative decreased. However, the simultaneous lengthening of TAU 2 indicates a negative lusitropic effect.

TABLE III Electrophysiologic Changes During Diltiazem Administration

		Time After Onset of Diltiazem Infusion (0.5 mg/kg^{-1} for 5 minutes, followed by 15 mg/hour)						
		Minutes						
Interval	Baseline	1	3	5	10	15	20	30
PQ (ms)	177 ± 11	172 ± 8	170 ± 8	180 ± 10	181 ± 11	183 ± 13	184 ± 12	184 ± 14
QRS (ms)	91 ± 5	87 ± 5	90 ± 5	87 ± 4	94 ± 6	94 ± 7	92 ± 6	96 ± 7
QT (ms)	405 ± 9	396 ± 9	394 ± 12	404 ± 9	413 ± 10	423 ± 13	417 ± 10	423 ± 12
QTc (ms)	412 ± 14	417 ± 12	424 ± 11	419 ± 8	421 ± 13	415 ± 12	411 ± 16	413 ± 15

supported by the reduction in positive dP/dt. However, the latter could also reflect a load-dependent effect because of the marked decrease in arterial pressures. In this respect, the isovolumetric velocity indexes, which are less sensitive to changes in afterload[18] or to moderate increases in left ventricular filling pressure[19] (as observed in the present study) did not indicate a reduction in contractility. In contrast, diltiazem negatively affected several relaxation parameters. Again, the decrease in negative dP/dt may have been secondary to the reduction in arterial pressures; however, this cannot explain changes in isovolumetric relaxation indices.[20,21] In the present study, each of the latter indexes increased, although only Tau_2 lengthened significantly. This suggests that, although diltiazem tended to reduce the rate of early relaxation, asynchrony of relaxation may have been induced as well.

Relation of hemodynamic changes and plasma diltiazem levels in patients with and without beta blockade: Maximal hemodynamic effects were observed at 5 minutes after onset of administration, at the end of the bolus infusion period, and concurred with peak diltiazem plasma levels. The levels obtained in this study were comparable to those previously reported by us, with a comparable dosage scheme in patients without β-blocking therapy, at least where the initial 5 minutes of infusion are concerned.[1] In contrast, the hemodynamic effects differed. In our previous study in untreated but otherwise comparable patients, a bolus infusion of 0.4 mg/kg administered over 5 minutes resulted in diltiazem plasma levels similar to those in the present investigation.[1] Likewise, systemic vasodilatation was comparable. However, subsequent reductions in left ventricular systolic and arterial pressures were less (12 vs 20% in the present study). Heart rate did not change after the moderate reduction in blood pressure, whereas in the present investigation a small, but significant increase in heart rate occurred despite the presence of β blockade. Also, in our previous study cardiac output improved significantly by 24%, in contrast to the present study. Finally, there were no changes in left ventricular filling pressure, compared with moderate elevations in the present investigation. These observations indicate that the acute hemodynamic effects of high-dose diltiazem, although acceptable, are less beneficial in patients with concomitant β-blocking therapy. How about different diltiazem dosage schemes?

Comparison with different dose regimens of diltiazem: In an equivalent model, in patients taking chronic β blockade, Kenny et al[5] investigated the effect of less than half the dose given in the present study. In their study only small reductions in systemic vascular resistance and arterial pressures were observed. Interestingly, heart rate decreased significantly, whereas cardiac output remained unchanged. Changes in the rate-pressure product were moderate. Also, coronary flow did not change in this study. In a comparable patient population, Rocha et al[6] investigated the hemodynamic effects of a bolus injection of 0.25 mg/kg diltiazem 5 and 15 minutes after drug administration. This dose regimen resulted in relatively low plasma diltiazem levels, 79 ± 26 μg/ml. In this study, a short-lasting increase in left ventricular filling pressure was observed, accompanied by a significant improvement in cardiac pump function. Heart rate did not change and contractility parameters remained unaltered, suggesting that a low-dose bolus injection without subsequent drug administration does not induce negative inotropic or chronotropic effects and is hemodynamically well tolerated in patients with a normal ventricular function at baseline. However, changes in arterial pressures were minor and cardiac work remained unaltered, suggesting no or only moderate reductions in myocardial oxygen demand.

Thus, whereas the hemodynamic tolerability of low-dose diltiazem is equal to or slightly better than high-dose administration, the effects on the myocardial oxygen demand/supply ratio are likely to be better with the latter dose regimen.

Hemodynamic effects of other calcium antagonists under similar conditions: Relatively few studies are available comparing the acute hemodynamic profile of different calcium antagonists in patients taking chronic β-blocking therapy. Intravenous verapamil induces dose-related negative chronotropic, dromotropic and inotropic effects and may decrease cardiac output, accompanied by significant increases in left and right ventricular filling pressures.[22,23] In contrast, sublingual nifedipine improves cardiac pump function as a result of its systemic unloading properties[22]; however, it may still induce some cardiodepressant effects.[24] The latter are absent with the new generation dihydropyridine derivatives. In a model similar to the one used in the present study, intravenous isradipine actually improved pressure-derived contractility parameters, irrespective of its chronotropic effect.[25] Preliminary data from similar studies with nicardipine and nisoldipine in patients taking β blockade indicate marked systemic neurohumoral activation paralleling the significant systemic vasodilating properties of these drugs and subsequent increments in heart rate and contractility indexes (unpublished observations). Although this may add to the prominent improvement in cardiac pump function after intravenous administration of these compounds, the concomitant increase in heart rate despite β blockade may limit their anti-ischemic potential.

Clinical implications: The moderate and short-lasting increase in heart rate with diltiazem in this study is unlikely to restrict its anti-ischemic potential. In contrast, diltiazem significantly reduced myocardial oxygen demand and cardiac work. As such, high-dose intravenous diltiazem may be expected to result in anti-ischemic effects in patients already treated with β-blocking agents and exposed to ischemic episodes at rest. The improvement in coronary flow, observed with high-dose but not consistently with low-dose intravenous diltiazem, is an additional argument in favor of such dose regimen in these patients. In addition to previous observations that high-dose intravenous diltiazem improves cardiac function in untreated patients with left ventricular dysfunction, the present study provides evidence that it is also well tolerated by and can be safely administered to patients taking long-term β-blocking therapy who have a normal ventricular function at baseline. The latter may not be true, however, when asymptomatic ventricular dysfunction or heart failure is present. The results of this acute study should not be extrapolated to conclusions regarding chronic therapy.

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Comparison of Coronary Responses to Intracoronary and Intraaortic Ergonovine and Isosorbide Dinitrate in Patients with Atypical Chest Pain

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Fifty patients with atypical chest pain were studied to compare coronary responses to intracoronary and intraaortic ergonovine. The diameters of the proximal, middle (1) and (2) (proximal segments of segments 2 and 3 [AHA classification], respectively), and distal segments of the right coronary artery were measured before and after intracoronary ergonovine (4 μg/minute over 4 minutes) and isosorbide dinitrate (ISDN) (2 mg) in 24 patients, and before and after intraaortic ergonovine (0.2 mg) and ISDN (5 mg) in 26. Mean vasoconstriction by intracoronary and intraaortic ergonovine were 13 ± 1.5% and 9 ± 0.8%, respectively ($p < 0.02$). Irrespective of the methods of administration, the responses to ergonovine were similar in the 4 segments. Mean vasodilation by intracoronary and intraaortic ISDN, which were used to quantify the degree of basal coronary tone, were 25 ± 2.2% and 27 ± 1.5%, respectively (p = not significant [NS]). There were significant negative linear correlations between the responses to ergonovine and ISDN in the middle (2) ($r = -0.51$; $p < 0.05$) and distal ($r = -0.53$; $p < 0.01$) segments in patients with intracoronary injection, and the proximal ($r = -0.41$; $p < 0.05$), middle (1) ($r = -0.66$; $p < 0.01$) and middle (2) ($r = -0.69$; $p < 0.01$) segments in patients with intraaortic injection.

These observations indicate that low-dose administration of intracoronary ergonovine produces sufficient coronary vasoconstriction, similar to or slightly greater than that of intraaortic ergonovine in patients with atypical chest pain, but basal coronary tone may influence the vasoreactivity to ergonovine.

(Am J Cardiol 1992;70:1004–1009)

Recently, direct intracoronary ergonovine was made available for provoking coronary spasm[1,2] and investigating the vasoreactivity in patients with chronic, stable angina[3] and atypical chest pain.[4] Although Kaski et al[5,6] reported the vasoreactivity, using the results combined with intracoronary and intravenous injection of ergonovine, there has been no report in which coronary response to intracoronary ergonovine is compared with the response to systemic (intravenous or intraaortic) injection.

On the basis of our previous finding that increased basal coronary tone may be part of the cause of ergonovine-induced spasm,[7–9] coronary response to ergonovine may be influenced by basal coronary tone.

In the present study, we compared the coronary response to intracoronary ergonovine with the response to intraaortic injection, and investigated the relation of vasoreactivities to ergonovine and isosorbide dinitrate (ISDN) in patients with atypical chest pain.

METHODS

Patient selection: Fifty patients referred for diagnostic coronary angiography to evaluate atypical chest pain were included in this study. All patients had normal or nearly normal coronary arteries after ISDN administration. No patient had prior myocardial infarction, valvular heart disease or cardiomyopathy. Patients with history suggestive of vasospastic angina were excluded from the study. Twenty-four patients (13 men and 11 women, aged 60 years, range 43 to 75) were administered ergonovine by intracoronary delivery (IC group), and 26 (18 men and 8 women, aged 50 years, range 34 to 64) were administered it by intraaortic delivery (IA group). Patients were older in the IC than in the IA group ($p < 0.01$). Written, informed consent was obtained from each patient.

Catheterization procedure: Coronary angiography was performed with the Judkins technique in the IC group and with the Sones technique in the IA group. Pharmacologic therapy was withheld for ≥24 hours before cardiac catheterization. After control coronary angiography was performed without premedication, ergonovine was administered in the right coronary artery by continuous infusion (4 μg/min over 4 minutes) in the IC group, and in the ascending aorta by bolus injection (0.2 mg) in the IA group. Coronary angiography was performed 4 minutes after ergonovine administration. Then, ISDN was administered in the right coronary ar-

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tery by bolus injection (2 mg) in the IC group, and in the ascending aorta by bolus injection (5 mg) in the IA group. Coronary angiography was repeated 2 to 4 minutes after ISDN administration.

Quantitative coronary angiography: The 35 mm cinefilm was projected with a Vanguard projector (model XR-35), and the selected cineframe was video-digitized in a matrix size of 512 × 512 with 8-bit (256 levels) brightness resolution and analyzed on a 14-inch videomonitor with approximately 2.5 magnification.

A circulating lesion of interest was positioned over a segment of the coronary artery, and the centerline of the segment was derived automatically. Linear density profiles perpendicular to the coronary artery centerline were extracted over the selected segment. Initial edge points were found by noting the density points with the first and second derivatives of the perpendicular density profile. These initial gradient-determined edge points were examined for spatial continuity, and outliers were discarded. Each perpendicular profile was then reanalyzed, and the locations of the final edge points were determined. The geometric diameter at any point along the centerline was the distance along each perpendicular profile between edge points on opposite sides of the coronary artery. The actual coronary diameter was determined by means of calibration, using the known catheter diameter. Particular care was taken to ensure that the measurements were obtained from exactly the same vessel segments.

The right coronary artery diameter was measured distal to the sinus node artery (proximal), right ventricular branch (middle [1]) and acute marginal branch (middle [2]), and immediately before the posterolateral branch (distal). Serial measurements were obtained at end-diastole in the 60° left anterior oblique projection of the right coronary artery.

Each coronary angiogram was analyzed in an identical fashion by 1 operator. Analysis of intra- and interobserver variability for 65 measurements of the coronary artery diameter showed high reproducibility ($r = 0.98$, SEE 0.23 mm, $p < 0.001$; and $r = 0.98$, SEE 0.15 mm, $p < 0.001$, respectively). Vasoconstriction by ergonovine and vasodilation by ISDN were calculated as follows: by ergonovine = control diameter − diameter after ergonovine/control diameter × 100%; and by ISDN = diameter after ISDN − control diameter/control diameter × 100%. Both control diameters used in these 2 equations were measured on the control angiogram.

Statistical analysis: All grouped data were reported as mean values ± SE. Paired and unpaired *t* tests were used to compare values between the 2 groups. Multiple comparisons of the groups were performed by 1-way analysis of variance. A linear regression analysis was performed to evaluate the relation between vasoconstriction by ergonovine and vasodilation by ISDN. A p value <0.05 was considered statistically significant.

RESULTS

Coronary responses to ergonovine: Control diameter and diameter after ergonovine of the 4 segments were similar between the 2 groups. In both groups, the diameter after ergonovine in the 4 segments was significantly smaller than the control diameter (Table I). The coronary diameters in the IC and IA groups were constricted by 8 ± 2.9% and 7 ± 1.6% at the proximal segment, 16 ± 3.1% and 9 ± 1.4% at the middle (1) segment, 14 ± 3.1% and 11 ± 1.9% at the middle (2) segment, 15 ± 3.0% and 8 ± 1.7% at the distal segment, and 13 ± 1.5% and 9 ± 0.8% in all segments, respectively (Figure 1). However, ergonovine dilated the diameter (≥5% change from control) in 11 of 96 seg-

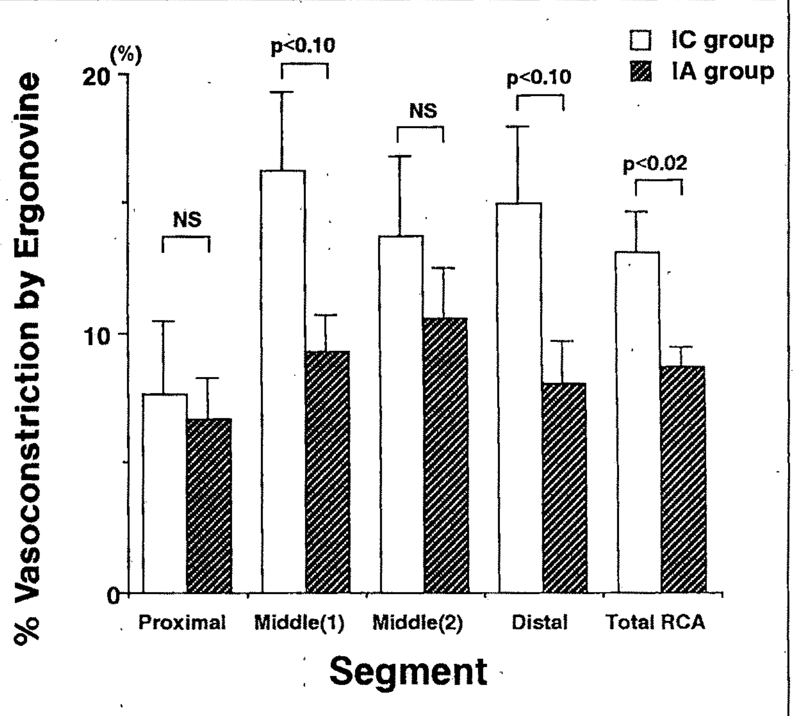

FIGURE 1. Coronary artery response to ergonovine shown as vasoconstriction by ergonovine. Vasoconstriction by ergonovine was compared between patients with intracoronary (IC group) and intraaortic (IA group) injection, and among 4 segments of right coronary artery (RCA). Values were not significantly different among 4 segments in both groups. NS = not significant.

TABLE I Diameter of the Right Coronary Artery on the Control Angiogram, and After Ergonovine and Isosorbide Dinitrate in 50 Patients

	Control Angiogram		After Ergonovine		After ISDN	
	IC Group (n = 24)	IA Group (n = 26)	IC Group (n = 24)	IA Group (n = 26)	IC Group (n = 24)	IA Group (n = 26)
Proximal	2.95 ± 0.69	3.02 ± 0.72	2.71 ± 0.66*	2.81 ± 0.68†	3.60 ± 0.73*	3.74 ± 0.93*
Middle (1)	2.72 ± 0.68	2.60 ± 0.55	2.31 ± 0.78*	2.34 ± 0.47*	3.36 ± 0.72*	3.30 ± 0.67*
Middle (2)	2.62 ± 0.83	2.32 ± 0.60	2.23 ± 0.69*	2.06 ± 0.51*	3.24 ± 0.97*	2.94 ± 0.74*
Distal	2.61 ± 0.70	2.32 ± 0.59	2.20 ± 0.65*	2.11 ± 0.50*	3.12 ± 0.80*	2.99 ± 0.94*

*$p < 0.01$; †$p < 0.05$ compared with diameter on control angiogram.
Values are reported as mean ± SD.
IA = intraaortic; IC = intracoronary; ISDN = isosorbide dinitrate.

ments (11%) with intracoronary injection and in 6 of 104 (6%) with intraaortic injection.

Thus, the values of the middle (1) and distal segments showed a tendency to be greater in the IC than IA group (both $p < 0.1$). There were no significant differences in the response to ergonovine in the proximal and middle (2) segments between the 2 groups (p = NS). The mean value of all segments was significantly greater in the IC than IA group ($p < 0.02$). By 1-way analysis of variance, in both groups, the vasoconstriction by ergonovine was not significantly different among the 4 segments.

Coronary responses to isosorbide dinitrate: The diameters after ISDN of the 4 segments were similar between the 2 groups. In both groups, the diameter after ISDN of the 4 segments was significantly larger than the control diameter (Table I). The coronary diameters in the IC and IA groups were dilated by 24 ± 3.8% and 24 ± 2.9% at the proximal segment, 26 ± 3.4% and 28 ± 2.5% at the middle (1) segment, 26 ± 5.4% and 29 ± 4.1% at the middle (2) segment, 22 ± 4.8% and 28 ± 2.6% at the distal segment, and 25 ± 2.2% and 27 ± 1.5% in all segments, respectively (Figure 2). However, ISDN constricted the diameter (≥5% change from control) in 5 of 96 segments (5%) with intracoronary injection and in 1 of 104 (1%) with intraaortic injection.

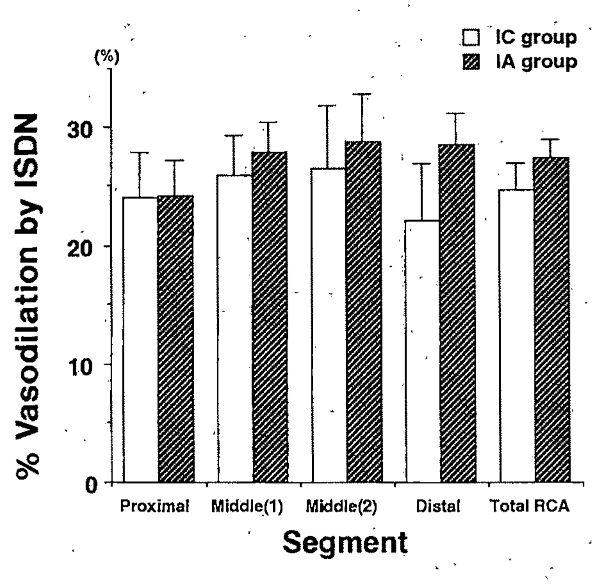

FIGURE 2. Coronary response to isosorbide dinitrate (ISDN) shown as vasodilation by ISDN. Vasodilation by ISDN was compared between patients with intracoronary (IC group) and intraaortic (IA group) injection, and among 4 segments of right coronary artery (RCA). There were no significant differences between 2 groups and among 4 segments.

Thus, there were no significant differences in the response to ISDN in the 4 segments between the 2 groups (p = NS). The mean value of all segments was similar between the 2 groups (p = NS). By 1-way analysis of variance, in both groups, the vasodilation by ISDN was not significantly different among the 4 segments.

Relation between coronary responses to ergonovine and isosorbide dinitrate: There were significant negative linear correlations between the vasoconstriction by ergonovine and the vasodilation by ISDN in the middle (2) ($r = -0.51$; $p < 0.05$) and distal ($r = -0.53$; $p < 0.01$) segments in the IC group (Figure 3), and the proximal ($r = -0.41$; $p < 0.05$), and middle (1) ($r = -0.66$; $p < 0.01$) and (2) ($r = -0.69$; $p < 0.01$) segments in the IA group (Figure 4), but no significant linear correlations between them in the proximal ($r = -0.06$; p = NS) and middle (1) ($r = 0.07$; p = NS) segments in the IC group (Figure 3), and the distal segment ($r = -0.22$, p = NS) in the IA group (Figure 4).

The vasoconstriction by ergonovine from the diameter after ISDN was 24 ± 3.1% and 24 ± 1.7% at the proximal segment, 32 ± 3.2% and 29 ± 1.0% at the middle (1) segment, 30 ± 2.7% and 30 ± 1.6% in the middle (2) segment, 29 ± 2.6% and 28 ± 1.7% at the distal segment, and 29 ± 2.9% and 28 ± 1.6% in all segments in the IC and IA groups, respectively. Thus, there were no significant differences in the responses in the 4 segments between the 2 groups (p = NS). The mean value of all segments was similar between the 2 groups (p = NS).

DISCUSSION

Recently, low-dose intracoronary administration of ergonovine was used to provoke coronary spasm, because it has only minimal effects on the systemic circulation and contralateral coronary artery.[1,2] However, with the increasing use of intracoronary delivery, quantitative analysis of vasoreactivity has been reported using the combined reactivity to intracoronary and intravenous ergonovine in patients with variant angina, coronary artery disease and atypical chest pain.[5,6] Although ergonovine produces a progressive and nonspecific dose-related reduction in coronary artery diameter in patients without coronary spasm,[10,11] there have been no studies in which coronary response to intracoronary er-

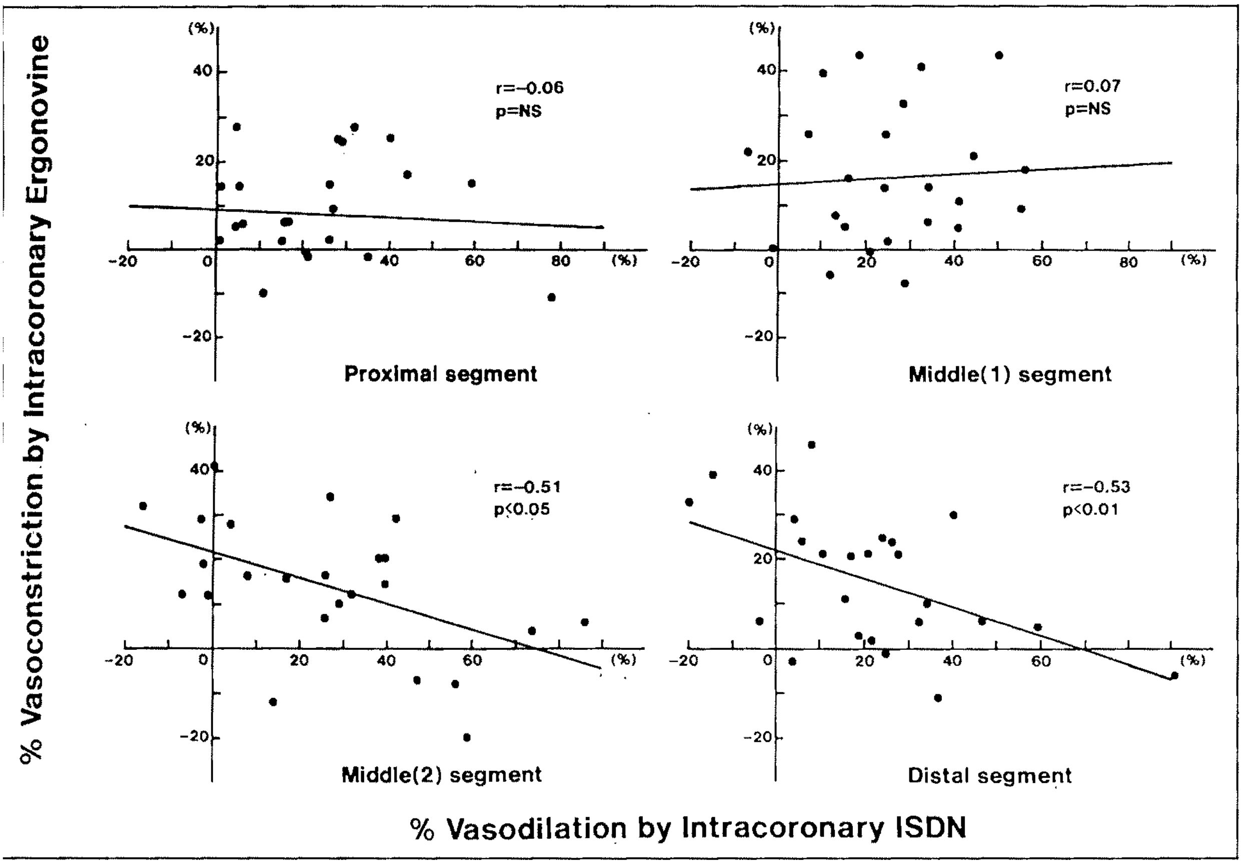

FIGURE 3. Relation between coronary response to intracoronary ergonovine and isosorbide dinitrate (ISDN) at proximal, middle (1) and (2), and distal segments of right coronary artery. NS = not significant.

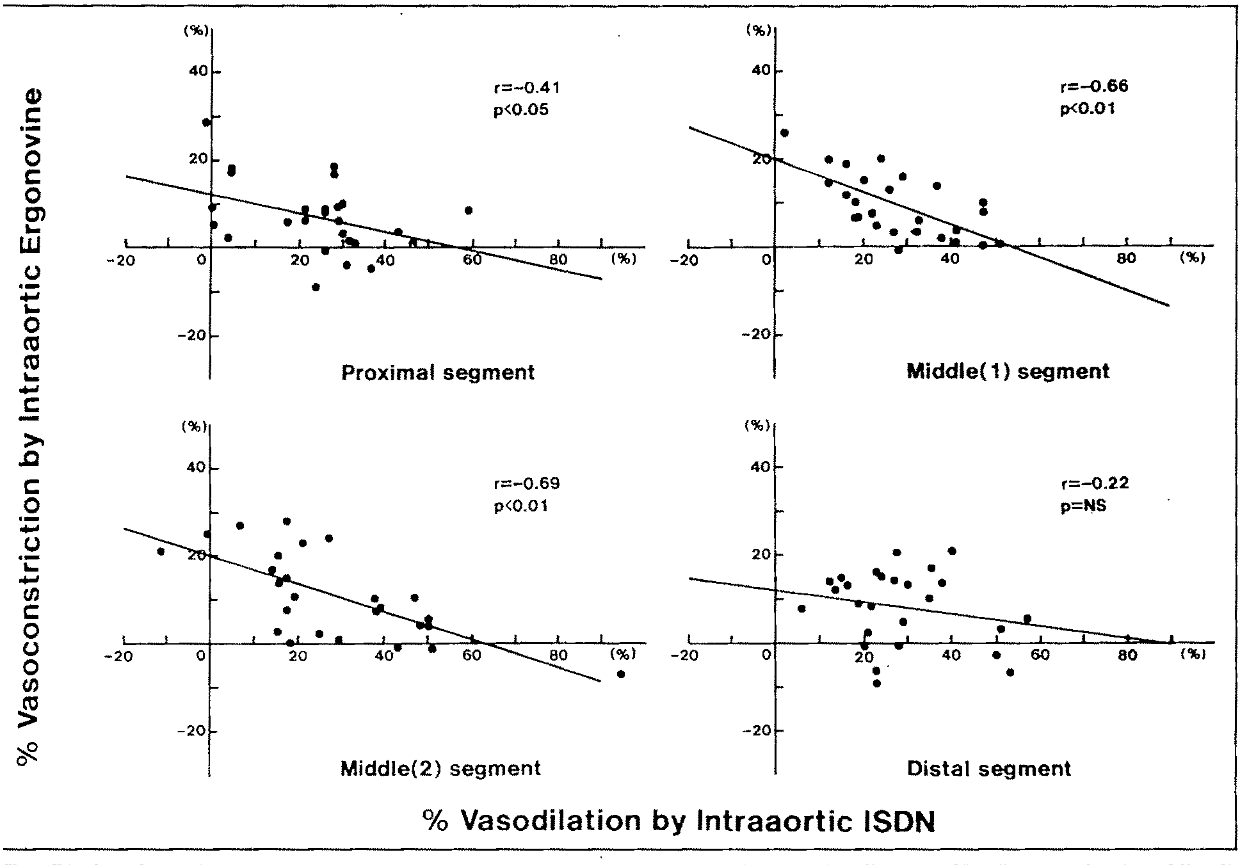

FIGURE 4. Relation between coronary response to intraaortic ergonovine and isosorbide dinitrate (ISDN) at proximal, middle (1) and (2), and distal segments of right coronary artery. NS = not significant.

gonovine was compared with the response to systemic (intravenous or intraaortic) injection.

Coronary response to ergonovine: In this study, the mean vasoconstriction by intracoronary and intraaortic ergonovine was 13 and 9%, respectively. However, ergonovine dilated 11 of 96 segments (11%) with intracoronary injection and 6 of 104 (6%) with intraaortic injection. Mohri et al[12] and Lambert et al[4] suggested that intracoronary ergonovine dilates the coronary artery with a lower dose and constricts it with a higher dose. As indicated by Holtz et al,[13] the coronary response to ergonovine may be biphasic, in the form of an initial dilating action followed by a constricting action. The vasodilative response to a low dose of ergonovine (which would stimulate the 5-hydroxytryptamine receptor)[14] would be similar to that observed after 5-hydroxytryptamine, probably mediated by the endothelium.[15]

There have been few studies of segmental response to ergonovine. Cipriano et al[10] reported that coronary vasoconstriction by intravenous ergonovine (0.4 mg) has the following small differences in the proximal, middle and distal segments: middle > distal > proximal in patients without coronary spasm. Tousoulis and Kaski et al showed that in patients with coronary artery disease, the distal normal segment has greater reactivity to intracoronary ergonovine than does the proximal normal one,[3] but the response to intravenous or intracoronary ergonovine is similar between proximal and distal normal segments in patients with atypical chest pain and coronary artery disease.[6,16] We showed that the coronary responses to both intraaortic and intracoronary ergonovine were not significantly different among the 4 segments of the right coronary artery, using 1-way analysis of variance. However, using unpaired *t* test, coronary vasoconstriction by intracoronary ergonovine had a tendency to be greater in the distal segment than in the proximal one ($p < 0.1$), but the response to intraaortic ergonovine was not significantly different between the proximal and distal segments. The differences for methods and doses of ergonovine administration may be related (at least in part) to the concentration of ergonovine to which a coronary artery segment was exposed. Intraaortic ergonovine would expose the full length of the coronary artery to the same ergonovine concentration over a long period of time. However, because of streaming and negligible ergonovine circulation, low-dose intracoronary ergonovine could produce poor contact of ergonovine with the coronary wall of more proximal segments, and better mixing and contact with the wall of more distal segments. Thus, segmental reactivity of the right coronary artery to intracoronary ergonovine may differ from that to systemic (intravenous or intraaortic) ergonovine.

Comparison of coronary responses to intraaortic and intracoronary ergonovine: The vasoconstrictive response to intracoronary ergonovine may be greater than that to the intraaortic injection. The patient's age may influence the coronary response to ergonovine, because patients with intracoronary ergonovine were older than those with the intraaortic injection ($p < 0.01$). Yasue et al[17] reported that there is a significant negative linear correlation between the coronary response to acetylcholine and the patient's age.

Furthermore, ergonovine concentration during intracoronary delivery may be higher than that during intraaortic delivery. Ishise et al[18] reported that ergonovine concentration during intracoronary delivery (8 μg/minute over 5 minutes) is significantly higher than during systemic administration (0.4 mg) in the coronary sinus.

Moreover, the magnitude of coronary response to ergonovine may be influenced by that of the basal coronary tone before ergonovine administration. The present study showed that there were significant negative linear correlations between the vasoconstriction by ergonovine and the vasodilation by ISDN in some segments. Theoretically, basal coronary tone before the administration of vasoactive drugs can vary by many intrinsic stimuli, even in patients with atypical chest pain. Lablanche et al[19] suggested that during coronary angiography, many stimuli can change coronary tone that by itself can vary during the day, and the index of total coronary vasomotion to ergonovine and ISDN (vasoconstriction by ergonovine plus vasodilation by ISDN) is useful to identify patients with abnormal vasomotor tone that can not be detected by conventional provocative tests. The present study showed that in all segments, the mean vasoconstriction by ergonovine from the diameter after ISDN was similar between intracoronary and intraaortic delivery, although the response to intracoronary ergonovine from the control diameter was greater than that to intraaortic injection. The findings that there were significant negative linear correlations between the vasoconstriction by ergonovine and the vasodilation by ISDN in some segments indicate that basal coronary tone may influence the reactivity to ergonovine.

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Treatment of Refractory Familial Hypercholesterolemia by Low-Density Lipoprotein Apheresis Using an Automated Dextran Sulfate Cellulose Adsorption System

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A subgroup of patients with familial hypercholesterolemia (FH) respond inadequately to standard diet and drug therapy, and are therefore at high risk for the premature development or progression of coronary artery disease. This study evaluated low-density lipoprotein (LDL) cholesterol and lipoprotein (a) removal in a multicenter, controlled trial with a new LDL apheresis procedure (Liposorber® LA-15 System). The study comprised patients with FH who had not responded adequately to diet and maximal drug therapy. There were 54 patients with heterozygous FH (45 randomized to treatment and 9 control subjects) and 10 with homozygous FH (all of whom received LDL apheresis). The study included three 6-week treatment phases and a 4-week rebound phase. Treatments were administered at 7- to 14-day intervals. Mean acute reductions in LDL cholesterol were 76% in heterozygous FH patients and 81% in homozygous ones. Time-averaged levels of LDL cholesterol were reduced 41% (243 to 143 mg/dl) in heterozygous FH patients and 53% (447 to 210 mg/dl) in homozygous ones. The substantial acute reduction of lipoprotein (a) (means: 65%, heterozygous FH; 68%, homozygous FH) has not been reported with other therapies. The Liposorber LA-15 System represents an important therapeutic option in FH patients who respond inadequately to diet and drug therapy.

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A subset of patients with heterozygous familial hypercholesterolemia (FH) and virtually all with homozygous FH do not achieve adequate low-density lipoprotein (LDL) cholesterol control with diet and drug therapy because of extremely high, initial lipid levels or drug intolerance. Surgical procedures such as partial ileal bypass, portacaval shunt and liver transplantation, although effective for lipid lowering,[1–3] have been associated with considerable morbidity. Plasmapheresis has been used to treat patients with severe FH,[4,5] but causes nonspecific depletion of plasma proteins, including high-density lipoprotein (HDL) cholesterol.

In contrast, LDL apheresis is an extracorporeal procedure that specifically removes apolipoprotein B–containing lipoproteins from the blood. Several LDL apheresis methods have been developed, including: (1) heparin-induced extracorporeal LDL precipitation,[6] (2) bags containing heparin-agarose,[7] (3) columns containing immobilized antiapolipoprotein-B antibodies,[8,9] and (4) columns containing immobilized dextran sulfate.[10,11] A recently developed LDL apheresis technique uses the Liposorber® LA-15 System (Kaneka Corporation, Osaka, Japan).[12] This method uses a hollow fiber cell separator and 2 disposable 150 ml columns containing dextran sulfate-cellulose beads. The advantages of this system include a small extracorporeal volume, nonsaturable lipid binding, disposable columns and absence of sensitization to column constituents as observed in patients undergoing immunoadsorption therapy.[13]

Preliminary uncontrolled studies using the Liposorber LA-15 System, and its precursor LA-40, which were conducted in Japan and Europe,[11,12,14–22] showed it to be a safe and effective method to selectively lower LDL. The present report describes the results from a multicenter, controlled trial of the Liposorber LA-15 System conducted in the United States in FH patients who were resistant to diet and maximal drug therapy.

METHODS

Study cohort: Patients of both sexes between the ages of 5 and 70 years who fulfilled the following criteria were eligible for the study: (1) FH heterozygotes who had LDL levels >160 mg/dl, despite appropriate diet and maximal tolerated combination drug therapy, or who were receiving an appropriate diet and had a

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ocumented history of drug intolerance; or (2) FH homozygotes. Diagnosis of heterozygous FH was based on he presence of primary hypercholesterolemia, tendon anthomas and family history of hypercholesterolemia. he diagnosis of homozygous FH included the criteria or heterozygous FH patients plus demonstration on ultured skin fibroblasts of <20% functional LDL reeptor activity.

Patients were excluded from the trial for the following reasons: pregnancy; body weight <15 kg or >30% bove ideal; severe cardiac disorders, such as malignant rrhythmias or decompensated congestive heart failure New York Heart Association functional class IV); nyocardial infarction or cerebrovascular accident in the revious 4 months; coagulation abnormalities; uncontrollable hypertension or hypotension; severe liver function abnormalities; diabetes mellitus; and any medical ondition that in the judgment of the investigator, may nterfere with safe apheresis treatment.

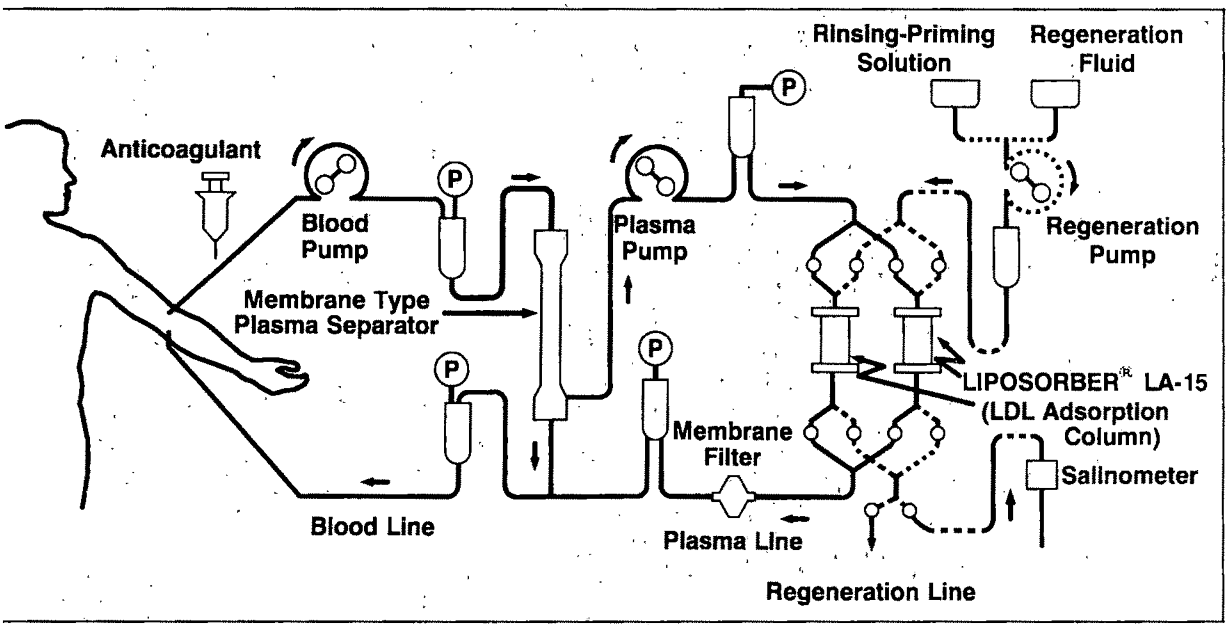
The study was approved by the institutional review oard of each participating center. All patients gave igned, informed consent. The Liposorber LA-15 System was granted investigational device exemption status y the Food and Drug Administration.

Study design: The study protocol comprised 2 hases: a 6-week screening phase, and a 22-week study hase that included an 18-week treatment period and a -week rebound period. During the 6-week screening hase, all patients were stabilized on diet (American Heart Association Phase I or a diet more restricted in aturated fats and cholesterol) and maximal tolerated rug therapy. Diet and drug therapy was continued unchanged through the study period. Patients with heterozygous FH were assigned at random to diet, drug therapy and LDL apheresis or to control (diet and drug therapy) in a 4:1 allocation. This allocation was adopted ecause lipid lowering in the treated group was expected to be so large that only a small number of control atients would be needed to demonstrate statistical significance of LDL cholesterol reduction. Randomization was stratified by clinical center and blocked within each center. Treatments could not be blinded, but assay of lipid, hematologic, biochemical and coagulation measures was performed by a central laboratory that was unaware of the treatment group assignment and clinical characteristics of patients.

The 18-week treatment period was divided into 3 time courses of 6 weeks each. LDL apheresis was performed once every 2 weeks during the first 6-week course. During the second and third 6-week courses, the treatment frequency was adjusted toward a time-averaged LDL level of 130 mg/dl in heterozygous FH patients and 160 mg/dl in homozygous ones. A 4-week rebound study followed the 18-week treatment period, during which LDL apheresis was discontinued to observe rebound in total and LDL cholesterol levels while patients received diet and drug therapy only.

LDL apheresis was performed in a continuous-flow manner using the Liposorber LA-15 System (Figure 1). Plasma separation from whole blood was performed using polysulfone hollow fibers in a 140 ml chamber with 1- to -1 and 1 half plasma volumes (50 to 70 ml/kg) processed per procedure. Sodium heparin was used as the anticoagulant. Two columns, each containing 150 ml of dextran sulfate cellulose, were used as the adsorbent for apolipoprotein B. Plasma was alternately perfused through each column, enabling regeneration of the off-line column with hypertonic (0.7 M) sodium chloride solution. The process was controlled by a computerized unit, thereby minimizing operator intervention. The plasma, after passing through the adsorbent column, was recombined with the cell stream and returned to the patient. Total extracorporeal volume was 400 ml. The columns were discarded after each treatment. For most patients, the treatment duration was 2.5 to 3.0 hours.

Lipid, lipoprotein and apolipoprotein determinations: All lipid, lipoprotein and apolipoprotein measure-



IGURE 1. Liposorber LA-15 System extracorporeal circuit. LDL = low-density lipoprotein; P = pressure sensor.

TABLE I Baseline Characteristics of All Patients*

	Heterozygotes			
	Treatment (n = 45)	Control (n = 9)	Homozygotes (n = 10)	All Patients (n = 64)
Mean age (year)	46	54	24	44
Male/female	29/16	5/4	3/7	37/27
Myocardial infarction (%)	14 (33)	3 (33)	0 (0)	17 (27)
Angina history (%)	30 (71)	7 (78)	5 (50)	42 (69)
Coronary bypass surgery (%)	23 (51)	3 (33)	3 (30)	29 (45)
Coronary angioplasty (%)	10 (22)	0 (0)	0 (0)	10 (16)
Cerebrovascular disease (%)	5 (11)	2 (22)	0 (0)	7 (11)
Peripheral vascular disease (%)	7 (16)	4 (44)	1 (10)	12 (19)
Hypolipidemic drugs taken (%)				
0	4 (9)	0 (0)	3 (30)	7 (11)
1	10 (22)	5 (56)	2 (20)	17 (27)
2	18 (40)	2 (22)	4 (40)	24 (37)
3	11 (25)	2 (22)	1 (10)	14 (22)
4	2 (4)	0 (0)	0 (0)	2 (3)
Drug received (%)				
Lovastatin	37 (82)	8 (89)	7 (70)	52 (81)
Resin	23 (51)	3 (33)	2 (20)	28 (44)
Niacin	22 (49)	2 (22)	3 (30)	27 (42)
Probucol	3 (7)	1 (10)	1 (10)	5 (8)
Gemfibrozil	2 (4)	1 (11)	0 (0)	3 (5)

*Includes all patients regardless of whether they completed baseline or treatment phases of protocol.

ments were obtained by a central laboratory (Medical Research Laboratories, Cincinnati). Total and HDL cholesterol and triglycerides were analyzed using microenzymatic procedures, as previously described.[23] The central laboratory maintained Centers for Disease Control–National Heart, Lung, and Blood Institute Part III Standardization for all 3 lipid parameters.[24] HDL was isolated using heparin-2 molar manganese chloride.[25] LDL cholesterol was calculated using the Friedewald formula: LDL cholesterol = total − HDL cholesterol − (triglycerides/5).[26] Total HDL and LDL cholesterol, and triglycerides were determined immediately before and after each treatment, and during the 4-week rebound period. Estimated values of LDL cholesterol were checked at baseline, and before and after treatment at 6-week intervals by direct measurements, using the ultracentrifuge.[27] Apolipoproteins A1, A2, B, E and lipoprotein (a) were measured using enzyme-linked immunosorbent assay procedures[28,29] twice in the 2 weeks before initial treatment, and before and after each treatment visit once every 6 weeks.

The time-averaged lipid levels for heterozygous FH patients randomized to the control group were calculated as the arithmetic average of lipids measured during the study period. To determine time-averaged levels for patients receiving LDL apheresis, measurements were performed between treatments in the first and second courses, and during the 4-week rebound period after the third course of therapy. Specimens for the rebound studies were typically sampled on days 0, 1, 2, 3, 5, 7 and 14. A simple arithmetic average of total or LDL cholesterol before and after treatment was not appropriate, because the rebound of lipid levels after LDL apheresis treatment followed a concave curve. Therefore, a time-averaged value was calculated using the area under the curve from values obtained during the rebound period.

Efficiency of adsorption: The efficiency of adsorption is a measure of the selectivity and adsorption specificity of the Liposorber LA-15 System for the different lipids and lipoproteins. For each treatment, regression analysis was used to generate a coefficient of adsorption efficiency (η) value for each lipid parameter. The following kinetic adsorption model was used:

$$C_{post} = \frac{V_p}{V_p + V_{e1}} * C_{pre} \exp\left(-\eta \frac{V}{V_p + V_{e2}}\right)$$

where C_{pre} is the pretreatment concentration of a parameter (mg/dl), C_{post} is the posttreatment concentration of a parameter (mg/dl), V_p is the estimated plasma volume (ml), V_{e1} is the extracorporeal volume + recovery solution (500 ml), V_{e2} is the extracorporeal volume, and V is the treated plasma volume.

Theoretically, a substance with an η of 0 passes through the LA-15 column with no adsorption, whereas a substance with an η of 1 is completely adsorbed onto the column. A mean η value for each lipid parameter was computed by averaging the η values of all LDL apheresis treatments.

Safety parameters: For each patient, a standard history and physical examination was performed before the beginning of the study. At each visit, an interim history, body weight and vital signs were recorded. Laboratory tests including hematology, coagulation, and biochemistry profiles, immunoglobulins and complement determinations were obtained at baseline, before the first 3 LDL apheresis treatments, and every 6 weeks thereafter.

Statistical analysis: Statistical analyses were performed by the data coordinating center (ADK Research Corporation, Pittsburgh). Baseline forms were collected by the treatment centers and forwarded to ADK Research Corporation. Baseline data were manually entered by double-entry verification in a data base created for the study on a DEC VAX 3100. Lipid and laboratory values were forwarded on diskettes to ADK Research Corporation from the central laboratory. SAS software (version 6, 1991, SAS Institute, Inc., Cary, North Carolina) was used in the statistical analysis of baseline and study data.

Patient characteristics and lipid values for homozygous and heterozygous FH control and treatment patients were compared for each group by *t* tests for continuous variables, such as lipid values, and by chi-square tests for categorical variables, such as gender. Two-tailed tests were used to calculate p values. A p value <0.05 was considered significant.

RESULTS

The clinical characteristics of all patients are listed in Table I. In all, 64 patients (37 male and 27 female, age range 8 to 67 years) enrolled in the study. The cohort included 54 patients with heterozygous FH, 45 of whom were randomized to receive LDL apheresis treatment and 9 to serve as the control group. Ten patients had homozygous FH, all of whom received LDL apheresis. Three homozygous FH patients had a prior surgial procedure to reduce the LDL level (ileal bypass n = 2] and portacaval shunt [n = 1]). One heterozyous FH patient randomized to receive LDL apheresis id not complete the baseline phase and never received DL apheresis. Nine heterozygous FH patients did not omplete the LDL apheresis protocol, because of inadeuate vascular access (n = 5) or adverse effects (n = 4). ne control subject was found to have nonfamilial hyercholesterolemia after randomization.

Coronary artery disease was clinically evident in nost patients enrolled in the study. The mean age of nset of symptomatic coronary artery disease was 38 ears. Cerebrovascular and peripheral vascular disease vere less frequently observed.

Baseline lipid values for all patients enrolled in the tudy are listed in Table II. Mean lipoprotein (a) levels vere increased (>40 mg/dl) in all groups. Despite diet nd combination lipid-lowering drug therapy, patients vith FH had mean LDL levels >200 mg/dl (heterozyotes) or >400 mg/dl (homozygotes). Many patients lso received concomitant medications such as calcium ntagonists (30%), β blockers (30%), nitrates (32%) and spirin (67%).

Acute lipid and apolipoprotein reduction: In all, 588 DL apheresis procedures were performed in 54 paients during the course of the study. The percent reducions in LDL cholesterol for the LDL apheresis treatnents ranged from 70 to 79% in the heterozygous FH atients and from 71 to 82% in the homozygous ones.

The overall mean acute reductions in LDL cholesterol were >75% for both heterozygous and homozyous FH patients (Table III). The mean acute reducions in total cholesterol were 61% (heterozygous) and 0% (homozygous). In contrast, the mean acute reducions in HDL cholesterol were only 5% (heterozygous) nd 13% (homozygous). Despite the acute reduction in IDL cholesterol, there was a 1 mg/dl increase in HDL holesterol levels before treatment over time for both eterozygous and homozygous FH patients. The mean cute reductions in lipoprotein (a) of 65% (heterozyous) and 68% (homozygous) were comparable to the ubstantial decreases in apolipoprotein B. As a group, omozygotes had significantly ($p < 0.05$) greater perent reductions in total, LDL and HDL cholesterol, and apolipoproteins A1, A2 and B than did heterozygous ones.

Efficiency of adsorption: LDL cholesterol had the highest η value (1.07 for heterozygotes, and 1.05 for homozygotes), indicating that it was most efficiently removed. In heterozygotes, the η values for lipoprotein (a)

TABLE II Mean Baseline Lipids (mg/dl) on Diet and Drug Therapy

	Heterozygotes			
	Treatment (n = 45)	Control (n = 9)	Homozygotes (n = 10)	All Patients (n = 64)
Total cholesterol	313 ± 54	285 ± 29	506 ± 145	339 ± 102
HDL cholesterol	48 ± 13	52 ± 16	39 ± 10	47 ± 14
LDL cholesterol*	239 ± 58	203 ± 34	447 ± 143	266 ± 108
LDL cholesterol†	239 ± 56	193 ± 54	447 ± 148	259 ± 104
Triglycerides	134 ± 47	148 ± 99	99 ± 53	130 ± 58
Apolipoprotein A1	125 ± 31	139 ± 25	100 ± 27	124 ± 32
Apolipoprotein A2	46 ± 11	46 ± 7	38 ± 11	45 ± 11
Apolipoprotein B	186 ± 44	153 ± 45	341 ± 100	203 ± 79
Apolipoprotein E	9 ± 2	10 ± 3	12 ± 4	9 ± 3
Lipoprotein (a)	43 ± 35	64 ± 63	47 ± 45	47 ± 41

*Estimated from Friedewald equation.[26]
†Directly measured.
Data are shown as mean ± SD and are inclusive of all patients enrolled in study regardless of whether they completed baseline and treatment phases of protocol.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

TABLE III Acute Mean Percent Reductions in Lipid, Lipoprotein and Apolipoprotein Levels

Lipid Parameter	Heterozygotes	Homozygotes	p Value*
Total cholesterol	61 ± 2	70 ± 4	0.0001
HDL cholesterol	5 ± 4	13 ± 5	0.0001
LDL cholesterol†	76 ± 2	81 ± 5	0.0281
LDL cholesterol‡	73 ± 4	78 ± 6	0.2032
Triglycerides	60 ± 9	59 ± 9	0.5716
Apolipoprotein A1	14 ± 4	19 ± 6	0.0026
Apolipoprotein A2	15 ± 7	23 ± 10	0.0363
Apolipoprotein B	63 ± 7	73 ± 5	0.005
Apolipoprotein E	56 ± 9	54 ± 40	0.7245
Lipoprotein (a)	65 ± 8	68 ± 11	0.3383

*Determined by analysis of variance for tests of effects of disease group.
†Calculated from Friedewald formula.[26]
‡Direct measurement.
Data are shown as mean ± SD and are inclusive of all patients enrolled in study regardless of whether they completed the protocol.
Abbreviations as in Table II.

TABLE IV Comparison of Baseline and Time-Averaged Mean Lipid Values (mg/dl)

	No. of Pts.	Baseline	Time Average*	p Value	Difference†
Total cholesterol					
Heterozygous FH					
Treatment	40	320 ± 54	220 ± 41	0.0000	−100 ± 46
Control	8	284 ± 31	317 ± 30	0.0484	+33 ± 18
p value		0.0794	0.0014		
Homozygous FH	10	506 ± 146	291 ± 83	0.0001	−216 ± 106
LDL cholesterol					
Heterozygous FH					
Treatment	40	243 ± 58	143 ± 39	0.0001	−100 ± 46
Control	8	206 ± 35	232 ± 37	0.1689	+26 ± 20
p value		0.0909	0.0059		
Homozygous FH	10	447 ± 143	210 ± 62	0.0001	−238 ± 111

*Time average for treatment patients calculated by area under curve method.
†Calculated as mean of all patients' differences between study period time-averaged lipid levels and mean baseline levels.
Patient number includes patients in treatment phase with sufficient data to calculate time-averaged levels.
FH = familial hypercholesterolemia; LDL = low-density lipoprotein.

and apolipoprotein B were similar (0.82 and 0.73, respectively). In homozygotes, the η values were 0.91 for lipoprotein (a) and 0.89 for apolipoprotein B. There was no evidence for HDL cholesterol removal by the columns, because the η values were −0.08 for heterozygotes and −0.06 for homozygotes. There were fewer differences between heterozygous and homozygous FH patients in η values than in acute lowering changes.

Time-averaged lipid changes: Forty-eight heterozygous FH patients (40 treatment and 8 control) and 10 homozygous ones had sufficient data to determine time-averaged changes in total and LDL cholesterol. In the 40 heterozygous FH patients, the time-averaged level of total cholesterol was reduced 31% (320 to 220 mg/dl), and LDL cholesterol was reduced 41% (243 to 143 mg/dl) (Table IV). In heterozygous FH patients, 42% achieved time-averaged total cholesterol levels <200 mg/dl, 75% had levels <240 mg/dl, and 50% had time-averaged LDL cholesterol levels <130 mg/dl. In homozygous FH patients, the mean time-averaged total cholesterol level was reduced 42% (506 to 291 mg/dl), and the LDL cholesterol level was reduced 53% (447 to 210 mg/dl). In homozygous FH patients, 40% achieved time-averaged total cholesterol levels <240 mg/dl. Although these levels were not as low as those achieved in heterozygous FH patients, the percent reduction was greater. In control patients, LDL cholesterol increased 13% from 206 mg/dl at baseline to 232 mg/dl during the study period. The difference in time-averaged LDL cholesterol levels between the treatment and control groups was highly significant ($p < 0.01$).

Time-averaged lipid levels were determined for the different time periods of the study to determine the effect of treatment frequency. The relation between LDL lowering and treatment frequency is shown for all patients in Figure 2. Pearson correlation analysis demonstrated a significant relation between frequency of therapy and reduction of time-averaged total and LDL cholesterol values ($p < 0.001$).

Rebound phase: During the 4-week rebound period, no statistically significant differences were observed between baseline and final rebound levels of total or LDL cholesterol in heterozygous and homozygous FH patients. In heterozygous FH patients, the last rebound LDL cholesterol level was 233 mg/dl compared with 240 mg/dl at baseline. In homozygous FH patients, the last rebound and baseline LDL cholesterol levels were both 447 mg/dl.

Safety: Adverse reactions were infrequent and similar to those found during any extracorporeal procedure. Hypotension, which occurred in 17 treatments (3%), was the most frequent adverse event; it was treated by temporary suspension of treatment, and infusion of saline solution. Avoiding medications immediately before the procedure that cause peripheral dilation was also effective in preventing hypotension in patients with a history of hypotension during the procedure. Lightheadedness or fainting (2 episodes), and nausea and vomiting (1 episode) were also observed. There were 3 episodes of hemolysis where pink-tinged plasma was noted in the tubing, but no clinical adverse effects occurred. There was 1 arrhythmia in a patient with history of coronary artery disease and chronic arrhythmias. Nine heterozygous FH patients withdrew from the study before completing the planned number of LDL apheresis treatments. Five patients discontinued treat-

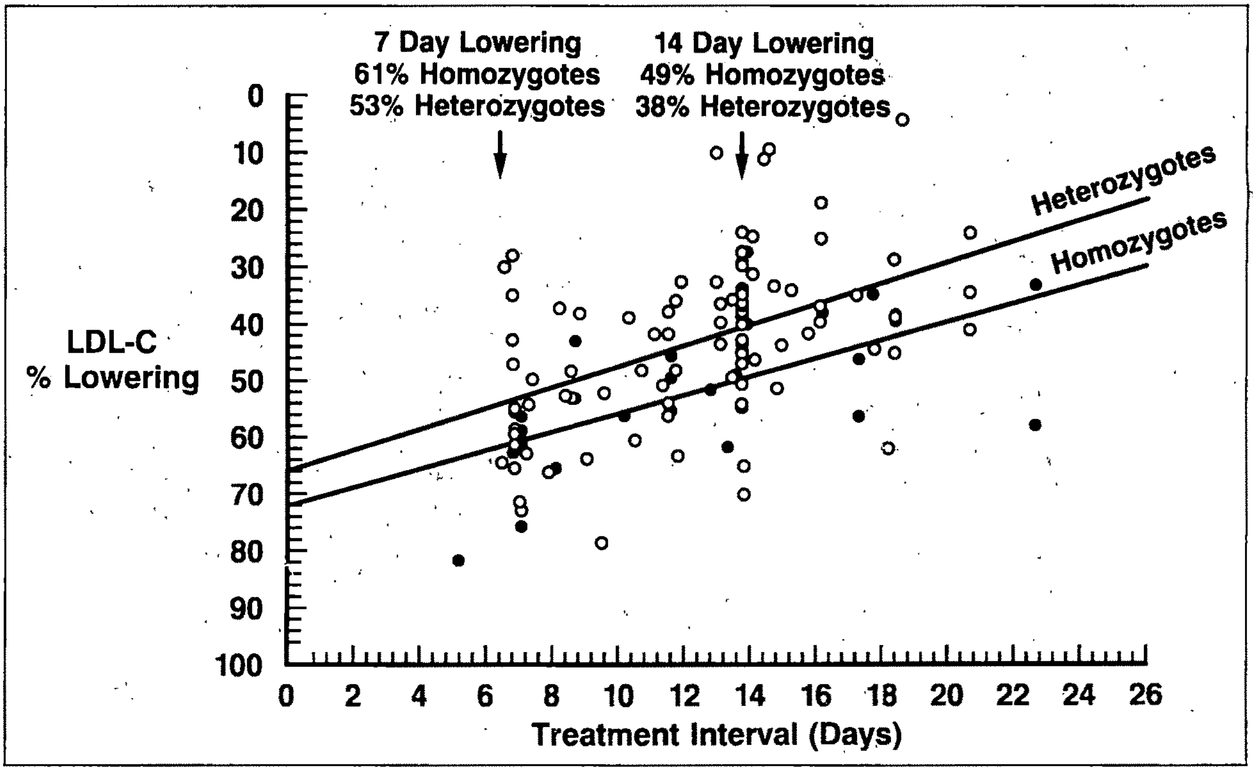


FIGURE 2. Relation between treatment frequency and low-density lipoprotein cholesterol (LDL-C) level for patients with homozygous *(closed circles)* and heterozygous *(open circles)* familial hypercholesterolemia.

ment because of difficulty in obtaining vascular access; 4 discontinued because of either hypotensive reactions (n = 1), headache, nausea and flushing (n = 1), arrhythmia (n = 1) or dietary noncompliance (n = 1).

There was no significant change in mean hematocrits during the study (baseline 42.2% for treated patients and 41.6% for controls; study period 40.5% for treated patients and 41.5% for controls). There was also no significant change in coagulation studies (baseline prothrombin time 12.5 seconds for treated patients and 12.6 seconds for controls; study period prothrombin time 12.7 seconds for treated patients and 13.3 seconds for controls). All other baseline hematologic, coagulation and biochemistry laboratory values also remained within the normal range throughout the study, and no significant differences in these values were found between patients receiving LDL apheresis and control subjects or between baseline and study period values.

DISCUSSION

The limited or invasive therapeutic options for patients with severe FH inadequately controlled on diet and maximal drug therapy have led to the development of LDL apheresis for removing apolipoprotein B-containing lipoproteins from the blood. The present study was designed to assess the efficacy and safety of LDL apheresis, using an automated dextran sulfate cellulose adsorption system.

This system was very effective in removing apolipoprotein B-containing lipoprotein particles; acute lowering of LDL cholesterol averaged 76% in patients with heterozygous FH and 81% in those with homozygous FH. The slightly greater lipid lowering observed in patients with homozygous FH most likely reflected a dilutional effect of the procedure, because of the smaller body weight and plasma volume of homozygous FH patients compared with those of heterozygous ones. The similarity of the LDL cholesterol binding efficiency of the columns between the patient groups supports this conclusion.

Repeated lowering of LDL by the procedure had little effect on underlying cholesterol metabolism during or after LDL apheresis therapy. Comparison of the LDL cholesterol value 4 weeks after discontinuing LDL apheresis treatment with the initial baseline level did not show an appreciable change. In contrast, the final LDL and total cholesterol values for the control patients showed an increase with time. There was a minimal increase in HDL cholesterol levels before treatment during the study. A prior report demonstrated that HDL-cholesterol levels may increase as a result of LDL apheresis therapy.[30] Plasma exchange, an alternative treatment in refractory FH patients, reduces HDL-cholesterol levels.

The acute lowering of lipoprotein (a) averaged 65 to 68%. This was consistent with the acute lowering of apolipoprotein B and indicated that the apolipoprotein (a) portion of the lipoprotein (a) molecule did not interfere with lipoprotein (a) binding to the dextran sulfate-containing columns. Reduction in lipoprotein (a) is particularly important for patients with FH, because of the close association between increased lipoprotein (a) levels and risk of atherosclerosis.[31] Standard diet and inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase do not reduce lipoprotein (a) levels.[32] Nicotinic acid when administered at a dosage of 4 g/day has been reported to decrease lipoprotein (a) levels by 34%.[33] LDL apheresis is the most effective method for markedly reducing lipoprotein (a) levels. Lowering of lipoprotein (a) by LDL apheresis using a heparin-induced LDL precipitation procedure was recently reported.[34] However, it remains to be seen whether reducing lipoprotein (a) also decreases the risk of coronary artery disease.

The results of this study help provide guidelines for the optimal treatment frequency for the procedure. Therapy every other week provides a substantial reduction of time-averaged LDL cholesterol levels (approximately 40% in heterozyotes and 50% in homozygotes). This treatment frequency should produce a time-averaged LDL level of ≤130 mg/dl in heterozygotes, provided that the initial LDL level on maximal drug therapy is ≤220 mg/dl. A once-weekly interval may be necessary in some patients with homozygous FH and a few with heterozygous FH to achieve desirable lipid levels.

The LDL apheresis procedure was well-tolerated by most patients. Difficulty with vascular access was a major problem in 5 patients. The observed adverse events were those associated and expected with all extracorporeal circulation procedures; hypotension was the most frequent event.

Randomized placebo-controlled studies in patients with hypercholesterolemia have shown that LDL lowering by diet and combination drug therapy can induce regression of coronary lesions.[35-37] Noncontrolled studies have suggested that LDL apheresis can induce regression of coronary lesions in patients with heterozygous and homozygous FH refractory to diet and drug therapy.[38-40] This clinical trial clearly demonstrated that the Liposorber LA-15 System safely and efficiently reduces LDL cholesterol and lipoprotein (a) levels in FH patients who have not responded adequately to diet and maximal drug therapy, and have few therapeutic alternatives.

APPENDIX

The participating centers and investigators were as follows: Abbott Northwestern Hospital, Minneapolis Heart Institute, Minneapolis, Minnesota: David C. Brown, MD, James H. Zavoral, MD; Baptist Memorial Hospital, Memphis, Tennessee: Kenneth D. Grosshart, MD, Thomas N. Stern, MD; Christ Hospital, Cardiovascular Research Center, Cincinnati, Ohio: Donald M. Black, MD, Evan A. Stein, MD, PhD; Evanston Hospital, Evanston, Illinois: Peter C. Dau, MD; Methodist Hospital and Baylor College of Medicine, Houston, Texas: Antonio M. Gotto, Jr, MD, Peter H. Jones, MD; National Institutes of Health, Department of Transfusion Medicine, Bethesda, Maryland: Susan F. Leitman, MD; Oregon Health Sciences University, Portland, Oregon: D. Roger Illingworth, MD, PhD, James S. Prihoda, MD; The Rogosin Institute, New York, New York: Bruce R. Gordon, MD, Daniel M. Levine, PhD, Thomas S. Parker, PhD, Stuart D. Saal, MD, Theodore

I. Tyberg, MD; and University of Texas Health Science Center, Dallas, Texas: David W. Bilheimer, MD, Ricardo Uauy, MD, Robert J. Zwiener, MD.

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Measurement of Ventricular Electrogram Amplitude During Intraoperative Induction of Ventricular Tachyarrhythmias

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Adequate sensing of ventricular tachycardia (VT) and ventricular fibrillation (VF) is necessary for proper functioning of an implantable cardioverter defibrillator (ICD). Several ICDs currently undergoing investigation have programmable fixed gain sensitivity for tachycardia detection. If intracardiac electrogram amplitude decreases below the programmed sensitivity during VT or VF, detection of a ventricular arrhythmia may be delayed or missed. The mean amplitude of intracardiac electrograms (ICEGM) recorded with bipolar epicardial or transvenous sensing leads was measured in 63 patients during induced VT and VF recorded in the operating room at the time of ICD implantation. The mean amplitude of the ICEGM during 41 episodes of VF in 15 patients decreased from 14.9 ± 0.9 mV during sinus rhythm to 8.8 ± 0.7 mV at 1 second, 9.7 ± 0.7 mV at 5 seconds, and 9.4 ± 0.7 mV at 10 seconds ($p <0.0001$ vs sinus rhythm ICEGM) with endocardial leads. The mean amplitude of the ICEGM recorded during 173 episodes of VF in 43 patients with epicardial leads decreased from 10.4 ± 0.3 mV in sinus rhythm to 7.8 ± 0.3 mV at 1 second, 8.3 ± 0.3 mV at 5 seconds and 8 mV at 10 seconds ($p <0.0001$ vs sinus rhythm ICEGM). The mean amplitude of epicardial and transvenous ICEGMs recorded during 34 episodes of monomorphic VT decreased from 18.5 ± 1.8 mV (epicardial) and 14.4 ± 2.0 mV (transvenous) during sinus rhythm ($p = 0.15$, epicardial vs transvenous) to 16.0 ± 1.7 mV (epicardial) and 13.7 ± 1.9 mV (transvenous) at 10 seconds (<10% of baseline amplitude). There was no significant difference between epicardial and transvenous ICEGM amplitude at 1, 5 or 10 seconds. Despite the absence of significant changes in mean ICEGM amplitude during time in VF, about 60% of episodes were associated with a 2 times or greater change in ICEGM amplitude during VF at each time measured. It is concluded that fixed gain devices must have sufficiently low programmable sensitivities to compensate for changes in ICEGM amplitude with time. Based on amplitude alone, there is a trend for transvenous electrodes to be superior to epicardial leads in providing higher amplitude signals during VF, but not during VT.

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The implantable cardioverter defibrillator (ICD) delivers therapy after a ventricular tachyarrhythmia is sensed. Reliable detection of ventricular tachyarrhythmias currently requires that the ventricular electrogram be of adequate amplitude within the given frequency range measured by the sensing amplifier of the ICD. Newer ICDs undergoing clinical investigation, such as the Guardian 4202/4203 and 4210 (Telectronics Inc., Denver, Colorado) and the PCD (Medtronic, Minneapolis, Minnesota) have programmable fixed gain sensing. If intracardiac electrogram amplitude is less than the programmed sensitivity, delayed or complete lack of detection of ventricular tachyarrhythmias may occur.

To assess the relation between ventricular electrogram amplitude throughout the duration of ventricular tachycardia (VT) and ventricular fibrillation (VF), we measured the amplitude of the ventricular intracardiac electrograms (ICEGM) at ICD implantation after induction of VF and VT at 1, 5 and 10 seconds following arrhythmia induction and during sinus rhythm. We also assessed the relation between ventricular electrogram amplitude during sinus rhythm to that measured during VT and VF. Finally, ICEGM amplitude during ventricular tachyarrhythmias was analyzed with respect to lead configuration (i.e., epicardial vs transvenous).

METHODS

We studied 63 consecutive patients undergoing ICD implantation at the Medical College of Virginia or the McGuire Veterans Affairs Medical Center from 1990 to 1991. All patients underwent implantation of a CPI Ventak 1550 or 1600 (Cardiac Pacemakers, Inc., St. Paul, Minnesota) or a Guardian 4202/4203 or Guardian ATP 4210. All patients gave written informed consent for intraoperative testing at the time of implantation. Our standard intraoperative testing includes testing for termination of VF at ≤20 J on 3 of 3 consecutive trials. The defibrillation shock was delivered after 11 to 13 seconds of VF. When the patients were clinically stable, VF was repeatedly induced and defibrillation thresholds were determined at lower energies. A minimal 2-minute rest period was interspersed between each episode of VF.

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TABLE I Clinical Characteristics of Patient Population

	No.
Men/women	60/3
Age (years)	60 ± 12 (21–85)
Ejection fraction (%)	32 ± 11 (10–55)
Underlying heart disease	
Coronary artery disease	50
Coronary artery bypass surgery	35
Previous acute myocardial infarction	40
Dilated cardiomyopathy (nonischemic)	8
Hypertrophic cardiomyopathy	1
Mitral valve prolapse	2
No structural heart disease	2
Clinical indications	
Cardiac arrest	17
Syncope	33
Refractory to antiarrhythmic medications	13
Induced arrhythmias	
Monomorphic VT	14
Polymorphic VT or VF	35
VT and VF	14

Values are mean ± SEM.
Numbers in parentheses are range.
VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE II Epicardial and Transvenous Intracardiac Electrogram Amplitude

Seconds	Epicardial (mV)	Transvenous (mV)	p Value
Ventricular Tachycardia			
Normal sinus rhythm	18.5 ± 1.8 mV	14.4 ± 2.0	0.14
1	15.7 ± 1.8	12.3 ± 1.9	0.20
5	18.0 ± 1.8	14.1 ± 1.9	0.13
10	16.0 ± 1.7	13.7 ± 1.9	0.37
Ventricular Fibrillation			
Normal sinus rhythm	10.4 ± 0.3	14.9 ± 0.9	0.001
1	7.8 ± 0.3	8.8 ± 0.7	0.20
5	8.3 ± 0.3	9.7 ± 0.7	0.05
10	8.0 ± 0.3	9.4 ± 0.7	0.07

p value: epicardial versus transvenous.

Rate sensing electrodes consisted of either a transvenous active fixation lead (Oscor Medical Corporation PY100BV or Telectronics Accufix, OF 040-113) placed in the right ventricular apex or a pair of bipolar epicardial screw-in electrodes (Possis model 052572, Medtronic model 6917-35T or Daig model 030-223) placed over the right ventricular outflow tract or apex. The screw-in electrodes were repositioned if the amplitude of the ventricular electrogram in sinus rhythm was <6 mV. In patients who had undergone cardiac surgery or were not undergoing additional procedures, an active fixation transvenous sensing lead (e.g., Oscor lead) was always used. In patients undergoing concomitant valve or bypass surgery, epicardial sensing leads were always used.

VF was induced by delivering 2 to 5 seconds of alternating current applied through the epicardial patches or rate-sensing leads. The mean ventricular electrogram amplitude was measured 1 second after alternating current was terminated, and again at 5 and 10 seconds after induction of VF. Electrograms were recorded and filtered through either the External Cardioverter Defibrillator II (CPI model 2806) or the External Testing Device (Telectronics model 4510). Electrograms were displayed on a VR-16 (Electronics for Medicine, Pleasantville, New York) and recorded at a paper speed of 50 to 100 mm/s. Calibration signals (5 mV amplitude) were delivered before induction of each episode of VF and after restoration of sinus rhythm. The amplitude of sinus rhythm electrograms was determined by averaging 5 consecutive beats, and the amplitude of electrograms during VF was measured by averaging the amplitude of 4 to 7 electrograms recorded during a 1-second interval at 1, 5 and 10 seconds after induction of VF or VT. When electrograms were fragmented, the portion of the electrogram with the greatest magnitude and greatest slope was measured. In general, a period of 120 to 150 ms was chosen before measuring the next electrogram to avoid measuring multiple peaks of the same electrograms.

Statistics: The relation between the intracardiac electrogram amplitude in sinus rhythm, VT and VF at 1, 5 and 10 seconds was compared with baseline values by repeated-measures analysis of variance for normally distributed data. Testing of epicardial versus transvenous amplitudes of ICEGMs and comparison between ICEGM amplitudes at 1, 5 and 10 seconds were done with a paired *t* test. A Bonferonni correction was made for multiple comparisons to the baseline. A probability level of <0.05 was considered significant. Linear regression (Pearson's correlation coefficient) was used to assess the correlation between electrogram amplitude during sinus rhythm and ventricular tachyarrhythmias. Continuous data were reported as mean ± standard error of the mean.

RESULTS

We studied 60 consecutive patients undergoing implantation of patches and epicardial or transvenous sensing leads at the time of initial intraoperative placement and 3 patients at the time of generator replacement. The clinical characteristics of our patient group are summarized in Table I.

Ventricular tachycardia: There were a total of 34 episodes of monomorphic VT observed in 14 patients. Each patient had a mean of 2.4 episodes (range 1 to 4). The cycle length of VT ranged from 240 to 360 ms (mean 288 ± 8). During 3 episodes, VF organized into monomorphic VT after 1 to 3 seconds, and ICEGM amplitudes of tachycardia were only measured at 5 and 10 seconds. Seventeen episodes of VT were recorded through epicardial leads, and the other 17 episodes with a transvenous sensing lead. The mean amplitude of the ICEGMs during VT are reported at 1, 5 and 10 seconds with both lead configurations (Table II).

The mean amplitude of ICEGMs during VT showed no significant change with time for either epicardial and transvenous leads. Most patients tended to have a ≤25% change in intracardiac electrogram amplitude over 10 seconds. The change in intracardiac electrogram amplitude from sinus rhythm to onset of VT was characterized by a ≤25% decrease in amplitude during 11 episodes, an increase or decrease in amplitude of ≤10% in 9 episodes, and an increase in amplitude of ≥10% for 11 additional episodes. These patterns had no relation to the sensing lead configuration (e.g., epicardial vs transvenous).

Ventricular fibrillation: There were a total of 173 episodes of VF recorded with epicardial leads and 41 episodes of VF with transvenous leads. There were 4 ± 1 episodes in patients with transvenous leads (range 3 to 7), and 4.3 ± 1 episodes in patients with epicardial leads (range 3 to 9). The mean amplitude of ICEGMs at 1, 5 and 10 seconds for epicardial and transvenous leads is listed in Table II and Figure 1. The mean ICEGM amplitude at baseline was 10.4 ± 0.3 mV for epicardial leads and 14.9 ± 0.9 mV for transvenous leads ($p = 0.001$). The mean ICEGM amplitude for epicardial leads was 7.8 ± 0.3 mV, and for transvenous leads was 8.8 ± 0.7 mV at 1 second ($p = 0.2$). At 5 seconds, the epicardial ICEGM amplitude was 8.3 ± 0.3 and 9.7 ± 0.7 mV for the transvenous leads ($p = 0.05$). At 10 seconds, the mean ICEGM amplitude was 8.0 ± 0.3 mV for the epicardial leads and 9.4 ± 0.7 mV for the transvenous leads ($p = 0.07$). The change in

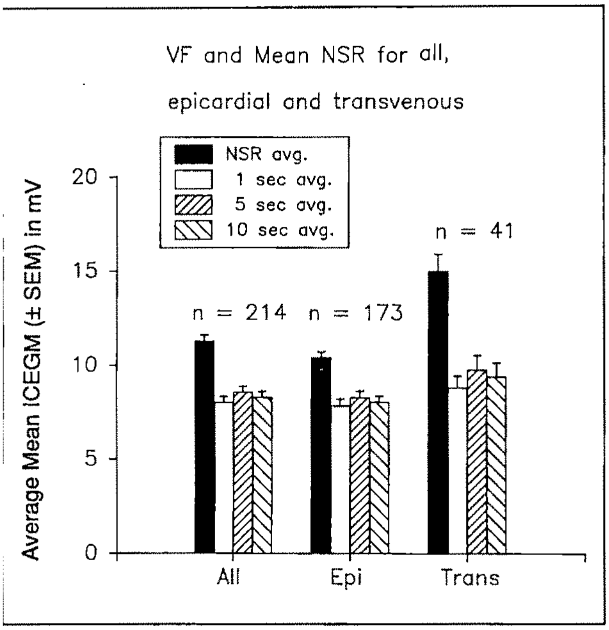

FIGURE 1. Mean amplitude of ventricular electrograms during ventricular fibrillation (VF) and normal sinus rhythm (NSR). Mean amplitude of intracardiac electrograms is calculated during ventricular fibrillation at 1, 5 and 10 seconds. Avg. = average; Epi = epicardial; ICEGM = intracardiac electrogram; sec = second; Trans = transvenous.

TABLE III Time-Dependent Changes in Ventricular Electrogram Amplitude During Ventricular Fibrillation

Pt. No.	Sensing (NSR-mV*)	1 Second Min.	1 Second Max.	5 Seconds Min.	5 Seconds Max.	10 Seconds Min.	10 Seconds Max.
1	Epi. (8)	2	5	3	5	2	6
		1	5	2	5	2	5
2	Epi. (8)	1	2	3	3	2	4
		2	6	2	3	3	6
		1	4	1	3	3	5
		6	9	3	6	3	5
		3	6	2	4	4	8
3	Epi. (7)	5	8	6	8	7	9
		2	3	2	5	2	7
		1	3	4	6	3	7
4	Epi. (14)	7	12	5	9	4	6
		2	8	3	7	6	10
		4	10	5	15	5	15
5		3	8	10	18	4	10
6	Epi. (10)	5	10	8	10	6	8
		5	7	6	8	8	10
7	Epi. (9)	5	8	7	8	4	8
		5	11	6	10	4	14
		6	8	7	20	7	8
8	Trans. (20)	15	20	18	22	18	25
		10	25	10	25	15	25
		12	18	15	20	8	15
9	Trans. (20)	2	6	2	5	4	10
		8	9	6	8	4	5
		4	7	4	9	2	4
		3	9	2	5	2	5
10	Trans. (24)	5	12	8	12	10	16
		4	8	14	18	10	15
		5	12	5	15	15	20
		3	10	10	18	10	20
11	Trans. (12)	8	14	8	10	8	15
		2	6	2	6	5	12
		6	15	8	15	5	15
		5	10	8	20	8	16
12	Epi. (17)	5	12	6	12	2	10
		5	11	5	15	2	8
		5	15	5	12	5	15
		6	19	10	14	5	19
13	Epi. (15)	5	10	5	8	3	7
14		12	20	4	10	3	8
		6	8	5	10	2	5
		12	16	7	12	10	13
15	Epi. (14)	8	16	8	18	8	14
		8	18	5	20	12	16
		10	20	15	25	5	25
		6	20	8	28	4	15
		12	20	8	20	5	15
16	Epi. (15)	10	20	10	14	7	12
		15	20	15	25	14	25
		15	25	20	22	20	22
		11	20	12	15	10	20
17	Epi. (9)	2	3	2	4	1	3
		1	3	1	3	1	3
		2	4	2	4	2	3
		2	4	2	3	1	3
18	Trans. (10)	5	8	4	9	5	12
		10	12	10	12	8	10
		4	8	10	11	10	12
		5	7	5	12	5	12
19	Epi. (14)	8	10	10	12	8	10
		14	16	14	17	14	17
		6	8	5	10	6	12
20	Epi. (12)	2	4	6	10	2	10
		1	3	6	10	2	5
		2	5	6	12	3	10
		3	6	6	8	4	7
21	Trans.(6)	1	10	1	2	<1	2
		2	4	<1	2	<1	2
		1	4	2	4	3	5

*The amplitude of the ventricular electrogram during normal sinus rhythm expressed in millivolts.

Epi = epicardial; Max. = maximal; Min.= minimal; NSR = normal sinus rhythm; Trans. = Transvenous.

ICEGM amplitude with time during VF is listed in Table III.

The correlation of amplitude of ICEGM in sinus rhythm with the amplitude of ICEGM during all ventricular tachyarrhythmias was r = 0.61 (p <0.00001) (Figure 2). The correlation of ICEGM amplitude in sinus rhythm with the ICEGM during VF was r = 0.19 (p <0.0001). The correlation between ICEGM amplitude during sinus rhythm and VT was better, r = 0.66 (p <0.00001). The correlation coefficients were not significantly improved when epicardial and transvenous ICEGMs were separately analyzed.

Variability within episodes: Approximately 25% of VF episodes showed a relatively small variability (<5 mV) in ICEGM amplitude. The remaining episodes showed considerable variability in ICEGM amplitude — increasing or decreasing ICEGM amplitude at 5 or 10 seconds compared with ICEGM amplitude at 1 second (Figure 3). About 60% of episodes showed a >50% change in ICEGM amplitude between 1 and 10 seconds. Of these episodes, 30% showed a 50 to 75% change and 10% a >75% change in ICEGM amplitude (Table III).

Variability between episodes in individual patients: All patients with VF had ≥3 episodes induced. There was considerable variability between different episodes in the same patient. In 50% of patients, a >5 mV change occurred in ICEGM amplitude or pattern of ICEGM amplitude change over time between individual episodes of VF. For example, 1 patient may have had little variability during 1 episode of VF and increasing or decreasing ICEGM amplitudes during episodes 2 and 3 (Table III).

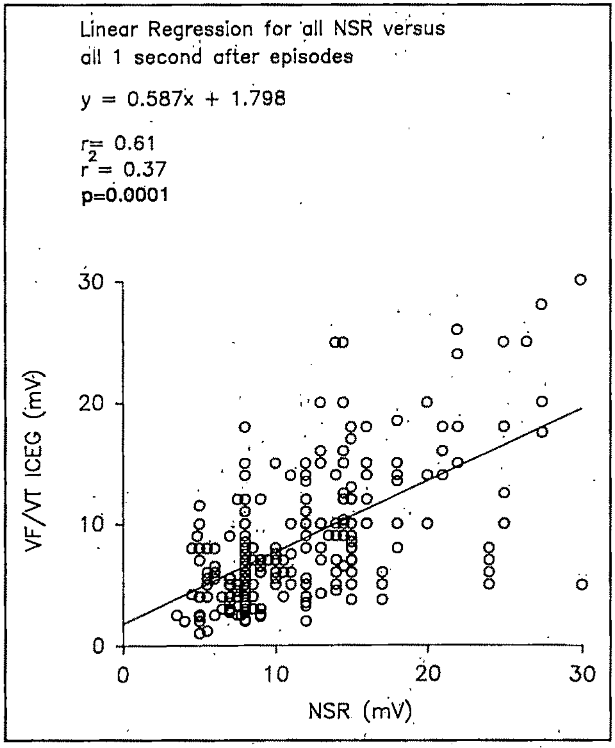

FIGURE 2. The correlation between intracardiac electrogram (ICEG) amplitude during normal sinus rhythm (NSR) and the first second of induced ventricular tachycardia (VT) or fibrillation (VF).

Intracardiac electrogram amplitude after an unsuccessful defibrillation shock: There were 25 episodes of VF during which the first shock did not cause conversion of VF to normal sinus rhythm. Analysis of ICEGM amplitude after the first shock did not show a decrease in ICEGM amplitude at 10, 15 or 20 seconds. There was no consistent pattern of change in ICEGM amplitude after an unsuccessful shock.

DISCUSSION

The major findings of our study are that mean amplitude of the ventricular electrogram during VT and VF are similar whether measured with transvenous or epicardial sensing leads. However, there was a trend for transvenous leads to record larger amplitude electrograms at 1, 5 and 10 seconds during VF only. The mean amplitude of the ventricular electrogram did not change significantly from 1 to 5 or 10 seconds after the induction of VF; however, there was considerable variation in electrogram amplitude in individual patients at 1, 5 and 10 seconds. There was also significant variation in ICEGM amplitude during different episodes of VF in the same patient. Finally, the correlation between VF and the sinus rhythm electrogram amplitude was poor, with significant variation seen between and among patients. It is unlikely that electrogram amplitude during sinus rhythm will be adequate for predicting ICEGM amplitude during VF.

ICDs must be capable of measuring signals that differ in amplitude by factors of 10- to 20-fold. Both pacemakers and defibrillators must have bandpass filters that eliminate sensing of unwanted signals such as T waves and external or environmental signals. Pacemakers, however, may have long refractory periods, whereas defibrillators are limited in refractory period durations because of the need to sense rapid tachyarrhythmias (RR intervals of 120 to 200 ms). Automatic gain control refers to the ability of an amplifier to sense signals of markedly differing amplitude by using an algorithm that allows amplifier gain to increase rapidly to a maximum if no signal is sensed, and to decline slowly following a sensed signal.

Another approach to avoid undersensing of ventricular tachyarrhythmias in devices with a fixed gain is to program the sensitivity of the ICD to a lower value. This may lead to detection of ventricular repolarization, T waves, and in occasional patients may still lead to signal dropout during polymorphic VT and VF. Saksena and Wilber both emphasized the importance of carefully assessing sensing during induced ventricular tachyarrhythmias in patients with fixed gain ICDs. They found that a significant percentage of patients had sensing problems when studied following implantation of the Telectronics Guardian 4202/4203, with failure to sense and signal dropout at some programmed sensitivities.[1-3] Most sensing problems were easily corrected by reprogramming the ICD's sensitivity or repositioning or changing sensing leads. In occasional patients, sensing problems necessitated removal of the ICD and replacement with one that has automatic gain control. We recently reported 2 patients in whom fixed gain sensing devices failed to recognize polymorphic VT or VF.[4]

There are several important limitations to this study that must be emphasized. Most patients in this study were enrolled at the time of intraoperative placement of sensing leads and patches. The long-term reliability of epicardial leads has been studied in some detail in children with permanent pacemakers and congenital heart disease, but has not been adequately studied in adults.[5-8] In children, the incidence of pacing exit block at 5 years varies from 18 to 45%.[5] In at least 1 series, epicardial leads lasted longer when implanted on the left ventricle rather than on the right ventricle.[5] The incidence of sensing problems is not specifically addressed in most of these studies.[5-8] In many studies, transvenous leads have fewer pacing threshold problems than epicardial leads.[7,9] Nevertheless, one cannot conclude that superior acute and chronic pacing thresholds will also result in superior acute and chronic sensing thresholds. The quality of chronic signals during VF may increase with time, emphasizing the importance of obtaining the "best" possible intracardiac signals at implant.

Sensing of an intracardiac signal depends on more than amplitude alone. The slew rate, or dV/dT is 1 determinant of the ability of an ICD or pacemaker to sense the ICEGM.[10] In addition, the frequency spectrum of the intracardiac electrogram will determine to what extent the signal will be altered by the high and low bandpass filters in the ICD. To accurately determine the ability of an ICD to sense a signal, the exter-

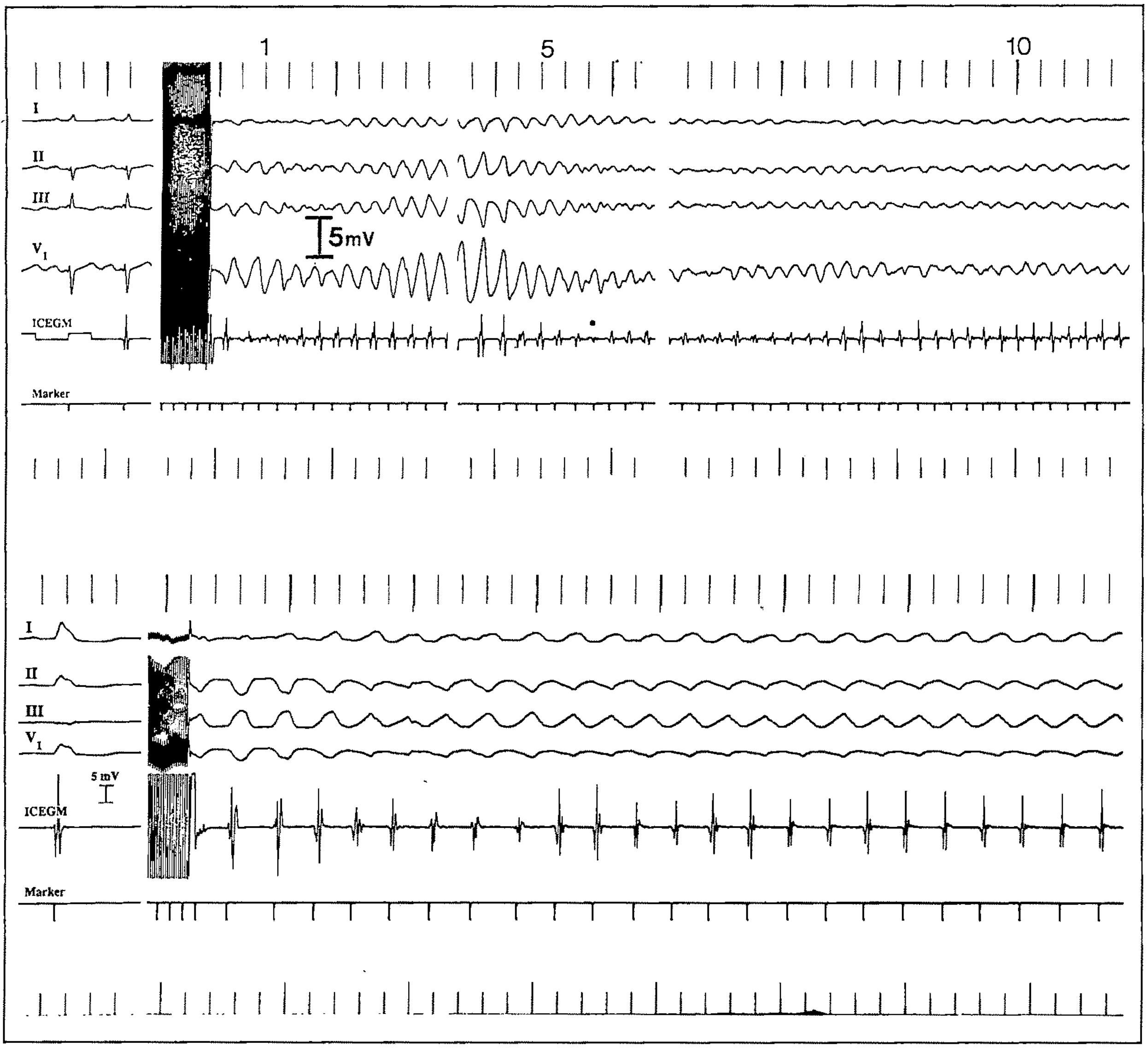

FIGURE 3. ***Top to bottom,*** **surface leads (I, II, III, V_1), intracardiac ventricular electrogram and marker channels during intraoperative testing in a patient with a dilated cardiomyopathy *(top)* and ischemic heart disease *(bottom)*. In the *top tracing,* changes in amplitude of ventricular electrograms is shown after induction of ventricular fibrillation with alternating current; a 5 mV calibration signal is shown after delivery *(top)* and before delivery *(bottom)* of alternating current. The intracardiac electrogram (ICEGM) amplitude is <5 mV at 1 second, varies from 3 to 10 mV at 5 seconds and is consistently >10 mV at 10 seconds. This contrasts with the typical behavior of intracardiac electrograms during ventricular tachycardia with a fairly constant amplitude of ICEGM at all times. Both sets of electrograms were recorded with a transvenous sensing lead.**

nal device analyzing signals must have identical filters as the ICD being implanted. Signal characteristics, such as slew rate and frequency content, play a significant role in determining how well the signal is sensed. An earlier study designed to measure ventricular electrogram amplitude during VF included only a small number of patients and did not include patients with transvenous sensing electrodes.[11] Future studies should use accurate measuring techniques by recording signal on tape and using digital signal processing software to analyze waveforms. Furthermore, the effect of antiarrhythmic agents on acute and chronic sensing thresholds should be determined. In some patients, it would be useful to compare transvenous and epicardial recordings during the same arrhythmia in a patient. Long-term studies that compare ICEGMs during ventricular tachyarrhythmias at the time of implant, at follow-up, and at the time of generator replacement must be performed. It is hoped that future studies will be able to analyze each of these variables and be better able to discern the relation between amplitude, frequency content and other signal characteristics such as slew rate. Left ventricular epicardial signals may provide better electrograms because the left ventricular mass is greater. The differences between right ventricular endocardial and left ventricular electrograms might be less. Finally, delivering of alternating current via the sensing leads may have changed or caused deterioration of electrograms. We do not believe this is the case, because electrogram amplitude was often greater at 1 or 5 seconds than at 10 seconds. Grubb et al[12] measured acute changes in pacing thresholds, electrogram amplitudes, slew rates and resistance before and after induction of $\geq$3 episodes of VF through rate sensing electrodes and noted no changes.

Kroll et al[13] published preliminary results suggesting that transvenous leads may be superior to epicardial leads for detecting VF. We have seen 1 patient in whom a transvenous lead failed to detect VF with a fixed gain sensing device. There are also several reports of patients who had sensing problems during VT or VF with one of the early Cardiac Pacemakers Inc. devices having automatic gain control.[14,15] In our study, ICEGM amplitude during VF tended to be better with transvenous than epicardial leads. The intracardiac signals from the transvenous leads appeared to be more easily measured than the signals recorded with the epicardial leads during VF. There was little difference in ICEGM amplitude from transvenous and epicardial leads during VT. Overall, the signals in VT were greater in amplitude than the signals recorded during VF. Long-term studies may ultimately discern whether the differences between epicardial and transvenous leads become larger, smaller, or do not change significantly over time. Finally, it would be important to compare electrogram amplitude directly with transvenous and epicardial leads in the same patient.

In summary, we were able to show that transvenous leads tend to record larger signals than epicardial leads during VF, but not during VT. The amplitude of the mean intracardiac electrogram does not significantly change with time during VF or VT. However, there is a significant change in ICEGM amplitude for most individual patients over time during VF, and in most patients this variability in ICEGM amplitude over time and between different episodes of VT/VF emphasizes the importance of careful measurement of ICEGM amplitude during intraoperative testing of ICDs.

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Effects of Chronic Amiodarone Therapy on Defibrillation Threshold

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In a prospective and parallel, randomized study, the long-term stability of epicardial defibrillation threshold was evaluated in 22 patients, using a patch-patch lead configuration at the time of implantation and generator replacement. The concomitant antiarrhythmic drug treatment consisted of either mexiletine (720 mg/day) or amiodarone (400 mg/day) and was administered to patients in a randomized and parallel manner. During a mean follow-up of 24 ± 6 months, the defibrillation threshold increased significantly from 14.3 ± 2.8 to 17.9 ± 5.3 J ($p < 0.05$) for the entire patient group. The increase in the chronic defibrillation threshold was due to a marked increase in defibrillation energy needs in the subgroup of patients receiving amiodarone. Whereas no significant change in the defibrillation threshold was documented in the subgroup of patients receiving mexiletine, the mean defibrillation threshold increased from 14.1 ± 3.0 to 20.9 ± 5.4 J ($p < 0.001$) in those receiving amiodarone. In all patients with increased defibrillation thresholds, reevaluation showed a reduction in the defibrillation threshold after discontinuation of antiarrhythmic drug therapy. The only variable associated with an increase in the chronic defibrillation threshold was amiodarone treatment. These findings suggest that the defibrillation threshold should be measured at each generator replacement and in case of a change in antiarrhythmic drug treatment. In particular, if amiodarone treatment is initiated, it is recommended that the defibrillation threshold should be reevaluated to ensure an adequate margin of safety.

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The implantable cardioverter-defibrillator has proved to be a safe and effective electrotherapeutic tool in the management of patients with life-threatening ventricular tachyarrhythmias.[1-5] Up to 70% of patients who receive an implantable cardioverter-defibrillator will also be maintained on concomitant antiarrhythmic drug treatment for a variety of reasons. Because antiarrhythmic drugs have been demonstrated to influence the defibrillation threshold, it is important to know whether the device will provide adequate energy for defibrillation during long-term follow-up and to what extent antiarrhythmic drug treatment will affect defibrillation energy needs.[6-14]

In regard to the long-term stability of epicardial defibrillation thresholds, there are only limited data available, which have led to controversial results.[15-17] Most previous reports were mainly concerned with patients who underwent implantation of a cardioverter-defibrillator with a transvenous spring electrode and left ventricular patch electrode configuration who were treated with various antiarrhythmic drug regimens. However, more important limitations are the obviously retrospective nature of those reports and the absence of a randomized design. Thus, we began a prospective and parallel, randomized study to determine if defibrillation thresholds are stable in patients with a patch-patch defibrillating lead system and if antiarrhythmic drug treatment is associated with a change in defibrillation energy needs.

METHODS

Study design: In this prospective study, 22 patients with drug refractory ventricular tachycardias were considered for implantation of a cardioverter-defibrillator. Written, informed consent was obtained from all patients. Before implantation of a defibrillator, mexiletine or amiodarone was prescribed to patients in a randomized and parallel manner. Mexiletine was administered in a dosage of 720 mg/day for 1 week and amiodarone in a dosage of 400 mg/day for a mean period of 12 ± 7 days after a loading phase of 1,000 mg/day for 14 days. Thereafter, patients underwent initial defibrillator implantation. All patients were maintained on the same antiarrhythmic drug therapy (mexiletine: 720 mg/day; or amiodarone: 400 mg/day) throughout the entire study. Defibrillation threshold testing was performed at the time of implantation and pulse generator replacement without changing the prescribed antiarrhythmic drug regimen. Furthermore, patients with increased defibrillation thresholds at the time of generator replacement were retested after either 3 months of amiodarone or 2 weeks of mexiletine discontinuation. To assess the

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TABLE I Patient Data

			Ejection Fraction (%)			DFT (J)			
Patient	Age (yr) & Sex	Cardiac Disease	At Implant	At Replacement	Antiarrhythmic Drugs	At Implant	At Replacement	After Drug Discontinuation	Replacement Time (mos)
1	34 M	CAD	33	30	Mexiletine	15	15		17
2	49 M	CAD	22	20	Mexiletine	20	20		26
3	52 F	CAD	35	35	Mexiletine	15	15		20
4	54 M	CAD	40	43	Mexiletine	15	20	15	19
5	54 M	CAD	26	28	Amiodarone	15	15		15
6	56 M	CAD	26	25	Mexiletine	15	15		22
7	57 M	CAD	40	38	Amiodarone	15	30	20	16
8	59 M	CAD	42	40	Amiodarone	15	15		36
9	59 M	CAD	29	30	Amiodarone	15	20	15	19
10	61 M	CAD	25	25	Mexiletine	10	10		21
11	62 M	CAD	35	32	Amiodarone	10	20	15	33
12	63 M	CAD	31	33	Mexiletine	10	10		24
13	63 M	CAD	53	55	Amiodarone	15	15		28
14	64 F	CAD	40	43	Amiodarone	10	20	10	26
15	70 M	CAD	28	30	Amiodarone	15	20	15	34
16	37 F	IDC	28	27	Mexiletine	15	15		26
17	43 F	IDC	25	25	Amiodarone	10	20	15	21
18	45 M	IDC	32	30	Mexiletine	15	15		17
19	48 M	IDC	18	17	Amiodarone	15	25	20	20
20	57 M	IDC	27	27	Mexiletine	15	15		28
21	59 F	IDC	30	30	Mexiletine	15	15		28
22	63 M	IDC	15	17	Amiodarone	20	30	20	23
Mean ± SD	55 ± 9		31 ± 8.6	31 ± 8.9		14.3 ± 2.8	17.9 ± 5.3		24 ± 6
Range	34–70		15–53	17–55		10–20	10–30		15–36

CAD = coronary artery disease; DFT = defibrillation threshold; IDC = idiopathic dilated cardiomyopathy.

influence of a progression in the underlying heart disease on the defibrillation threshold, noninvasive and invasive techniques (including echocardiography and cardiac catheterization with contrast ventriculography) were performed in all patients before defibrillator implantation and after pulse generator replacement.

Study cohort: Clinical data of patients are summarized in Table I. The underlying heart disease was coronary artery disease in 15 patients and dilated cardiomyopathy in 7. Mean left ventricular ejection fraction as assessed by contrast ventriculography was 31 ± 9% (range 15 to 53%). All patients had survived ≥1 sudden cardiac death, and 18 had recurrent episodes of ventricular tachycardia. The mean replacement time of the pulse generator was 24 ± 6 months, (range 15 to 36). The surgical approach was a median sternotomy in all patients. Concomitant coronary artery bypass grafting was performed in 10 patients. The implanted defibrillator system consisted of a Ventak pulse generator (CPI, St. Paul, Minnesota) and a patch-patch lead configuration in all patients. Two large epicardial patch electrodes were implanted in 17 patients, and the combination of a large and a small epicardial patch electrode was used in 5. There was no difference in the frequency of coronary bypass surgery and the use of various patch size systems between patients treated with amiodarone and mexiletine.

Defibrillation threshold testing: All defibrillation threshold measurements were obtained using an external cardioverter-defibrillator (CPI) that delivers a truncated exponential shock waveform that is identical to that of the automatic implantable cardioverter-defibrillator. Defibrillation threshold testing was performed in the operating room with the use of general anesthesia. Ventricular fibrillation was induced by brief application of alternating current. Ventricular fibrillation was defined as a sinusoidal, irregular rhythm with a change in amplitude and a rate >200 ms that did not support any evidence of phasic blood pressure. For determination of the defibrillation threshold, only true episodes of ventricular fibrillation were evaluated; induced episodes of polymorphic or monomorphic ventricular tachycardia were not analyzed in this study. After 15 seconds of ventricular fibrillation, the initial shock with an energy of 15 J was delivered. If successful, the energy was decreased stepwise by 5 J until defibrillation was ineffective. All unsuccessful attempts were immediately followed by a 40 J rescue shock. If the initial 15 J shock was ineffective, the energy was increased stepwise by 5 J until defibrillation was achieved. Defibrillation trials were separated from one another by approximately 5 minutes. The lowest successful shock energy was repeated once. The defibrillation threshold was defined as the lowest energy needed for successful defibrillation on 2 occasions.

Statistical analysis: Student's *t* test for paired variables was used to compare defibrillation thresholds and left ventricular ejection fractions. Multivariate analysis was performed to examine which factors were associated with an increased defibrillation threshold. Analysis of variance was used to compare patients treated with amiodarone and mexiletine. All data are expressed as mean ± SD. A p value <0.05 was considered significant.

RESULTS

Defibrillation threshold: The defibrillation threshold for the entire group increased significantly from 14.3 ± 2.8 J at the initial implantation to 17.9 ± 5.3 J at the time of replacement ($p < 0.05$). For further analysis, the study cohort was separated in 2 groups: patients receiving mexiletine and those receiving amiodarone. Figure 1 illustrates the comparison of the defibrillation thresholds of the 2 groups. At the time of implantation, the defibrillation threshold did not differ significantly between both groups. However, at the time of generator replacement, the mean defibrillation threshold increased significantly ($p < 0.001$) in the amiodarone group compared with in the mexiletine group. Whereas no change in defibrillation threshold could be documented in patients receiving mexiletine (14.5 ± 2.7 J at implantation vs 14.8 ± 2.9 J at replacement), the mean defibrillation threshold increased significantly ($p < 0.001$) from 14.1 ± 3.0 J at the time of implantation to 20.9 ± 5.4 J at the time of replacement in the subgroup of patients receiving amiodarone.

Multivariate and univariate analyses were performed to assess a predictive value for the demonstrated increase in the chronic defibrillation threshold. The evaluated parameters included age, gender, cardiac disease, presenting arrhythmia, number of previous ineffective antiarrhythmic drug trials, left ventricular ejection fraction, concomitant coronary bypass grafting, type of current antiarrhythmic drug treatment, serum concentrations of amiodarone and desethylamiodarone, time between implants and number of delivered shocks during follow-up. The only variable that was found to be associated with an increase in the chronic defibrillation threshold was the use of amiodarone ($p < 0.05$). Serum concentrations of amiodarone and its major metabolite desethylamiodarone were measured when defibrillation threshold testing was performed. All measured serum concentrations of amiodarone and desethylamiodarone were within therapeutic range. At implantation, mean serum concentrations of amiodarone and desethylamiodarone were 1.4 ± 0.6 and 1.1 ± 0.3 ng/ml, respectively, and at replacement 1.7 ± 0.6 and 1.4 ± 0.5 ng/ml, respectively. No significant difference could be found in serum levels of amiodarone or desethylamiodarone between the times of implantation and replacement.

In all patients, noninvasive and invasive procedures (chest x-ray, echocardiography and angiography) were performed to exclude a progression in the underlying heart disease. Based on these results, no significant change in left ventricular ejection fraction could be found in patients (Table I). Biplane chest x-ray showed no dislocation or crinkling of the epicardial patch electrodes, which may influence the energy needed for successful defibrillation. All patients with increased defibrillation thresholds underwent reevaluation of the defibrillation threshold after either 3 months of amiodarone or 2 weeks of mexiletine discontinuation. All patients had a decrease in the defibrillation threshold, but only 4 returned to the initial defibrillation threshold (Table I).

DISCUSSION

With the increasingly widespread use of the implantable cardioverter-defibrillator, there are major concerns whether the defibrillation threshold remains stable over time and whether any factors may be associated with increased defibrillation energy needs. There have been controversial reports regarding the stability of the epicardial defibrillation thresholds.[15-18] In an animal study using a spring-patch lead configuration, a significant decrease in the defibrillation threshold occurred between days 1 and 11 after lead implantation.[18] Thereafter, energy needs for successful defibrillation remained stable until termination of the study on day 32. However, those results could not be confirmed in 2 studies in which no significant change in defibrillation energy needs was observed in patients, using either a spring- or patch-patch lead system over a mean follow-up period of 17 months.[16,17] However, a significant increase in the

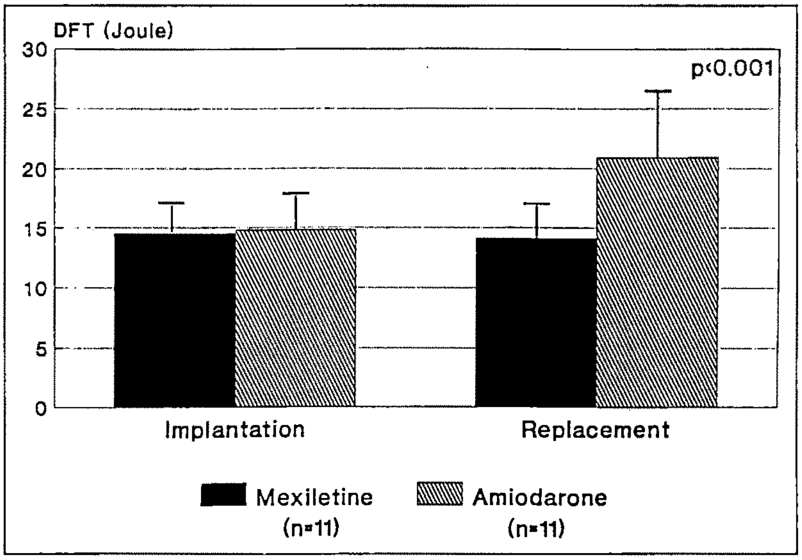

FIGURE 1. Comparison of defibrillation threshold (DFT) at times of implantation and generator replacement. Patients were separated into 2 groups receiving either mexiletine (n = 11) or amiodarone (n = 11). At replacement, DFT increased significantly (p <0.001) in amiodarone group compared with in mexiletine group.

defibrillation threshold from 12.3 to 16.9 J has been demonstrated in patients with a spring-patch lead system during a follow-up period of 24 months.[15]

In the present study, a significant increase (14.3 ± 2.8 to 17.9 ± 5.3 J) could be demonstrated in patients, using a patch-patch lead configuration during a mean follow-up of 24 months. In accordance with the results of Guarnieri et al,[15] we found a marked increase in the defibrillation threshold at the time of generator replacement in the subgroup of patients receiving chronic amiodarone. Furthermore, we did not observe any differences in the defibrillation threshold levels in patients at the initial implantation. In contrast to these findings are data that show that higher defibrillation energies were needed at the initial implantation in patients receiving amiodarone.[19] Amiodarone-induced refractoriness to internal defibrillation has been reported in a patient in whom a 40 J shock was unsuccessful in terminating ventricular fibrillation while the patient was receiving chronic amiodarone therapy.[20] Three months after discontinuation of amiodarone, defibrillation was accomplished with 10 J. All our patients were retested 3 months after discontinuation of amiodarone therapy. In each patient, the defibrillation threshold decreased, but only 4 returned to the initial defibrillation threshold at implantation. For safety reasons, a sufficient defibrillation threshold margin should be considered in patients undergoing implantation of a defibrillator. Although the safety margin was reduced in some patients at the time of generator replacement, it can be assumed that a currently available implantable defibrillator capable of delivering a 30 J shock would likely have converted each patient's arrhythmia, with the possible exception of 3 patients presenting with borderline defibrillation thresholds >20 J. However, there are no systematic data available with regard to the long-term follow-up and survival of patients presenting with borderline defibrillation thresholds.

The effect of amiodarone on the defibrillation threshold has been a controversial issue.[12-16,19-21] It appears that amiodarone reduces the defibrillation threshold acutely, but chronically may increase the threshold. The specific pharmacokinetics of amiodarone and its metabolite provide an explanation for the delayed onset of its antiarrhythmic action and may explain the increase in defibrillation thresholds in our patients receiving chronic amiodarone therapy.[22]

Apart from amiodarone, other antiarrhythmic drugs may also alter the defibrillation threshold.[6-11,13,14] One of 11 patients receiving mexiletine had an increase in the chronic defibrillation threshold. Such an increase in the defibrillation threshold after oral administration of mexiletine has been reported in 1 patient at the time of defibrillator implantation.[10]

Multivariate analysis revealed that the only predictor for an increased chronic defibrillation threshold was amiodarone treatment. A progression in the underlying heart disease as a cause for increased defibrillation thresholds was excluded in all patients by noninvasive and invasive studies at the time of generator replacement. Furthermore, the defibrillation threshold was not affected by concomitant bypass surgery.

Study limitations: The clinical determination of the defibrillation threshold as a single quantity of energy is probably a misleading concept and is better described by its percent success rate. This probability function of defibrillation is best expressed by a sigmoidal dose-response curve.[23-25] The accuracy of our defibrillation threshold measurements using increments or decrements of 5 J is limited because an actual small change in the defibrillation threshold can produce an apparent increase of 5 J. However, the constraints of defibrillation threshold testing in patients make the application of a large number of shocks clinically and ethically unjustifiable. Therefore, we and other investigators have used a modified form of defibrillation threshold testing to express the defibrillation success rate.[15,16,19] Because of the number of patients studied, there may be some deficiency with respect to the statistical analysis used. Thus, further studies involving a larger patient population are necessary to confirm the present findings. The results of this study are specific for the patch-patch lead configuration and the truncated exponential waveform applied by the external cardioverter-defibrillator. Therefore, these results may not be applicable to other defibrillation waveforms or defibrillating lead systems. These results should be reevaluated in patients, using endocardial lead systems and biphasic shock waveforms.[26]

Clinical implications: The data show a significant increase in the defibrillation threshold in the subgroup of patients receiving chronic amiodarone over a mean period of 24 ± 6 months, but do not demonstrate when the change in the defibrillation threshold occurred. Because it is still unknown when the determination of the defibrillation threshold should be repeated in patients treated with amiodarone, we suggest that retesting should be performed in these patients 3 and 6 months after amiodarone is initiated to ensure an adequate margin of safety. Since other antiarrhythmic drugs may also alter defibrillation energy needs, reevaluation of the defibrillation threshold is recommended if antiarrhythmic drug treatment is changed. Furthermore, it appears advisable to reexamine the defibrillation threshold at the time of pulse generator replacement to ensure continued effectiveness.

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Beta-Blocking Effect of Propafenone Based on Spectral Analysis of Heart Rate Variability

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RR variability was analyzed in 15 patients with ventricular arrhythmias to evaluate whether the antiarrhythmic action of propafenone is associated with alteration of neural control mechanisms. Before drug administration, spectral analysis of RR variability was characterized by 2 major components at low and high frequency, which are considered to reflect sympathetic and parasympathetic modulation of the heart period. After propafenone (600 to 900 mg/day), there was a marked reduction in RR variance (826 ± 184 to 412 ± 77 ms^2; $p < 0.05$), although the mean RR interval was unchanged. The drug significantly reduced the low-frequency component (52 ± 6 to 28 ± 4 nu) and augmented the high-frequency component (39 ± 6 to 55 ± 5 nu). As a result, the low-/high-frequency ratio (an index of sympathovagal balance) decreased from 2.0 ± 0.4 to 0.6 ± 0.1. A positive correlation between serum levels and drug-induced changes in the low-frequency component was also observed. Furthermore, the increase in the low-frequency component induced by tilt (53 ± 5 to 79 ± 3 nu) was markedly attenuated after drug administration (27 ± 5 to 54 ± 7 nu). Thus, propafenone administration is associated with changes in spectral components that are consistent with a β-blocking effect of the drug.

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The absence of evidence that suppression of ventricular arrhythmias in patients after myocardial infarction[1] may determine a reduction in mortality demands the development of new approaches to evaluate the indications for the use of antiarrhythmic drugs and for a better understanding of their mechanisms of action.[2]

It is well established[3,4] that frequent and complex ventricular arrhythmias, as well as low ejection fraction, constitute independent risk factors for cardiac mortality after myocardial infarction. Furthermore, clinical and experimental evidence indicates[5–9] that a surge in sympathetic activity may facilitate the development of ventricular tachycardia and fibrillation. Alterations in neural control mechanisms were also considered to be present to explain the finding that both reduced RR variability[10,11] and depressed baroreflex sensitivity[12,13] were associated with an increased cardiac mortality and arrhythmic events in patients after myocardial infarction.

Although antiarrhythmic drugs are frequently used in these patients, little attention has been given to the evaluation of the effects of these drugs on the indexes of sympathetic and vagal neural regulatory activities. In the present study we evaluated whether the antiarrhythmic effects of propafenone[14] (a class 1C drug structurally related to β-adrenergic antagonists)[15] were associated with changes in sympathovagal interaction assessed by spectral analysis of heart rate variability.[16]

METHODS

Study group: We studied a group of 15 consecutive patients treated with propafenone. History of sustained ventricular tachycardia or fibrillation was documented in 7 cases, whereas symptoms related to frequent ventricular ectopic beats were present in 8. Eight patients had had a myocardial infarction (>1 year previously); of the remaining 7 subjects, 5 had mitral valve prolapse and 2 hypertensive heart disease. All subjects were in sinus rhythm and were not receiving medications known to affect heart rate variability parameters, such as β blockers, digoxin, calcium antagonists and angiotensin-converting enzyme inhibitors. Left ventricular end-diastolic diameter and ejection fraction were determined by 2-dimensional echocardiography. The day before the recording, 24-hour Holter monitoring was performed in control conditions and during administration (9 to 15 days) of propafenone (600 to 900 mg/day) that was considered effective when a 90% reduction of ventricular premature beats and complete suppression of repetitive ventricular arrhythmias were observed.

Study protocol: Informed consent was obtained in accordance with the requirements of the committee for the protection of human subjects from research risks at

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the University of Milan. All recordings were obtained in the late morning, with the subject lying comfortably on a bed in a warm and quiet environment. After 10 minutes for stabilization, an electrocardiographic lead with a prominent R wave and a respiratory signal originating from a nasal thermistor were continuously recorded on magnetic tape (Racal) for 20 minutes in control conditions and during chronic administration of propafenone. In the last 10 patients, recordings were also obtained during 90° head-up tilt.

To establish the drug level, blood samples were collected from 10 patients immediately after the recording session, approximately 4 hours from the last morning dose. Samples were analyzed by high-performance liquid chromatography.[17]

Data analysis: Off-line analysis was performed with a Microvax 3500 minicomputer. Electrocardiographic and respiratory signals were played back from the FM tape and digitized at 300 samples/s per channel. The principles of the software for data acquisition and analysis were previously described.[16,18,19] Briefly, stationary sections of data of appropriate length were selected for analysis. To satisfy the need for stationary conditions required by spectral analysis,[16] the following procedure was used: After identification of each QRS complex, the program first calculated the tachogram that was then visually inspected to recognize the step changes due to premature ventricular contractions and manually edited by substituting the mean pre- and postextrasystolic RR intervals with 2 averaged values. Series of 150 to 250 RR intervals were considered adequate for further analysis when editing was limited to ≤5 events; otherwise, data were disregarded. This resulted in 2 patients with frequent ventricular premature contractions having no RR interval series suitable for analysis from the entire recording period before drug administration.

From a section of the tachogram with a length of 150 to 250 RR intervals, simple statistics (mean and variance) of the data were computed. The computer program then calculated the autoregressive coefficients necessary to define the power spectral density estimate and provided the number, amplitude and center frequency of the oscillatory components. As previously reported in normal subjects during resting conditions, spectral analysis of heart rate variability has 3 major components: a very low frequency component (0 to 0.03 Hz) not addressed in the present study, and 2 additional components at low (0.1 Hz) and high (0.25 Hz) frequency. Each spectral component is presented in terms of frequency (Hz) and amplitude, which is determined by its area and measured in absolute value as squared milliseconds. The power of each component was also expressed in normalized units (nu) that were obtained by dividing the power of a given component by the total variance (from which the very low frequency component was subtracted) and multiplying by 100. With these algorithms, the duration of periodical phenomena in the variability signal was measured as a function of cardiac beats, rather than in seconds. However, this frequency is easily converted into Hz equivalent by dividing it by the average RR interval length. The respiratory signal (sampled once for each cardiac cycle) was analyzed with the same algorithm to determine the respiratory frequency and facilitate the identification of the high-frequency component of RR variability, which was synchronous with respiration.

Statistical analysis: Data are presented as mean ± SE. Analysis of variance was used to assess the effects of propafenone on RR variability parameters. Student's *t* test for paired observations was used to determine the significance of the difference between rest and tilt. Linear regression analysis was used to evaluate the relation between plasma concentration of propafenone and amplitude as well as changes of the low-frequency component induced by the drug. Contrasts were considered significant when a p value <0.05 was observed.

RESULTS

Propafenone administration (average dose 730 ± 29 mg/day) was associated with a significant reduction in premature ventricular complexes (403 ± 179 to 24 ± 2/hour) and with suppression of all repetitive beats. No changes in arterial pressure were observed after drug administration. Left ventricular end-diastolic diameter and ejection fraction during propafenone therapy were 54 ± 2 mm and 61 ± 5%, respectively. No patients presented clinical signs of congestive heart failure.

Effects of propafenone on RR variability: Propafenone did not produce any modification in mean RR interval (877 ± 33 to 875 ± 34 ms), whereas RR variance was significantly reduced (826 ± 184 to 412 ± 77 ms^2) (Figures 1 and 2, and Table I). Before drug administration, spectral analysis of RR variability was characterized by 2 major components at low (0.10 ± 0.02 Hz) and high (0.27 ± 0.01 Hz) frequency (Figure 1), the latter being synchronous with respiration. The low-frequency component was predominant (52 ± 6 vs 39 ± 6 nu) with a low-/high-frequency ratio of 2.0 ± 0.4. After propafenone, we observed a significant reduction in the low-frequency component (−23 ± 4 nu) and a marked increase in the high-frequency component (17 ± 4 nu) (Figure 1). As a result, the low-/high-frequency ratio diminished to 0.62 ± 0.12 (Figure 3). Similar values were obtained when the ratio was calculated using the absolute power of spectral components, which was markedly reduced after propafenone as a result of the decrease in RR variance.

Plasma concentration of propafenone was 840 ± 153 ng/ml. Whereas plasma levels and amplitudes of the low-frequency component were unrelated, there was a significant correlation between plasma levels and the observed reduction in the low-frequency component (Figure 4).

Effects of propafenone on the response of spectral indexes to 90-degree head-up tilt: Before drug administration, tilt was associated with a significant reduction in RR interval (832 ± 39 to 717 ± 29 ms), whereas RR variance was unchanged (Table II). Spectral analysis revealed a marked increase in the low-frequency component (53 ± 5 to 79 ± 3 nu) and a reduction in the high-frequency component (38 ± 5 to 12 ± 2 nu) (Figures 5 and 6). As a result, the low-/high-frequency ratio increased from 1.79 ± 0.46 to 11.9 ± 5.0. After propafenone, we observed a similar reduction in the RR interval,

TABLE I Effects of Propafenone on Measures of RR Variability

	RR (ms)	Variance (ms^2)	LF (ms^2)	LF (nu)	LF (Hz)	HF (ms^2)	HF (nu)	HF (Hz)	LF/HF Ratio
Before propafenone (n = 13)	877 ± 33	826 ± 184	330 ± 118	52 ± 6	0.10 ± 0.02	171 ± 36	39 ± 6	0.27 ± 0.01	1.98 ± 0.45
After propafenone (n = 15)	875 ± 34	412 ± 77*	56 ± 25*	28 ± 4*	0.09 ± 0.01	80 ± 20*	55 ± 5*	0.24 ± 0.02	0.62 ± 0.12*

*Significantly different contrast ($p < 0.05$) between before and after propafenone.
HF = high-frequency component; LF = low-frequency component.

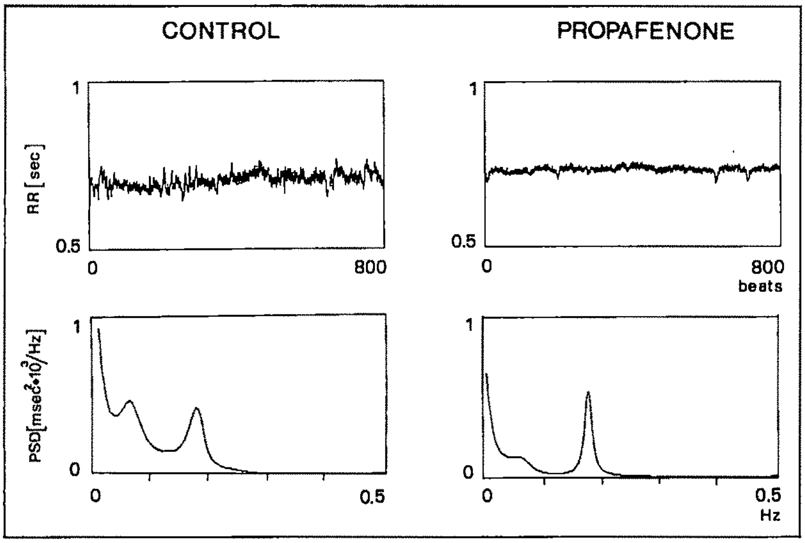

FIGURE 1. Effects of propafenone on spectral analysis of RR variability. Tachograms *(top)* and autospectra *(bottom)* before *(left)* and after *(right)* propafenone are displayed. Note marked reduction in low-frequency and increase in high-frequency components after drug administration. PSD = power spectrum density.

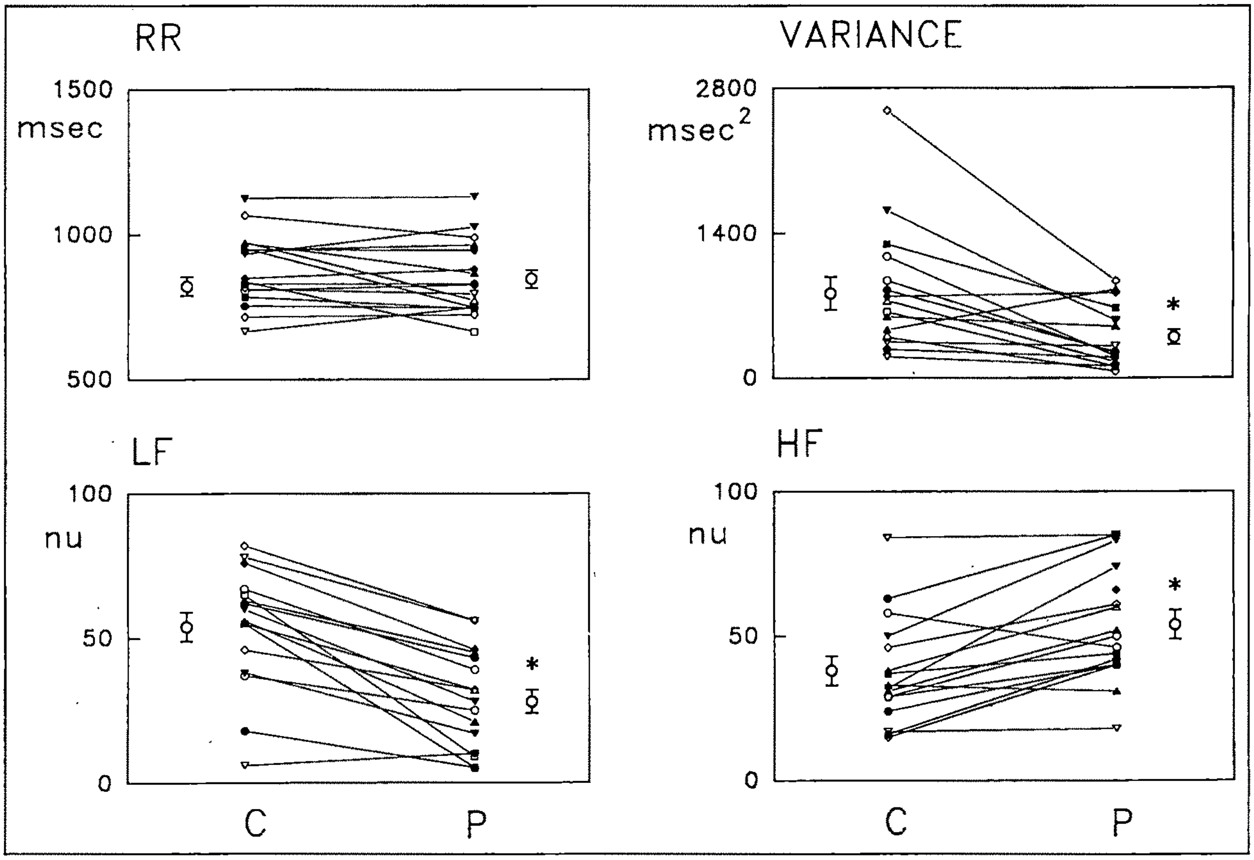

FIGURE 2. Effects of propafenone on RR interval, variance, and low-frequency (LF) and high-frequency (HF) components of RR variability in individual patients. C = control; P = after propafenone; *p <0.05.

TABLE II Effects of Propafenone on Measures of RR Variability During Tilt

	RR (ms)	Variance (ms^2)	LF (ms^2)	LF (nu)	LF (Hz)	HF (ms^2)	HF (nu)	HF (Hz)	LF/HF Ratio
Before propafenone (n = 8)									
Rest	832 ± 39	601 ± 132	215 ± 75	53 ± 5	0.08 ± 0.01	172 ± 58	38 ± 5	0.26 ± 0.02	1.79 ± 0.46
Tilt	717 ± 29*	679 ± 189	391 ± 171	79 ± 3*	0.07 ± 0.01	62 ± 30	12 ± 2*	0.29 ± 0.03	11.9 ± 5.0*
After propafenone (n = 10)									
Rest	844 ± 34	347 ± 71	33 ± 10†	27 ± 5†	0.08 ± 0.01	72 ± 25	48 ± 6	0.25 ± 0.02	0.80 ± 0.28
Tilt	744 ± 24*	229 ± 47†	52 ± 13†	54 ± 7*†	0.09 ± 0.01	39 ± 17	33 ± 7*†	0.20 ± 0.01†	4 ± 1*

*Significantly different contrast between rest and tilt ($p < 0.05$); †significantly different contrast before and after propafenone.
Abbreviations as in Table I.

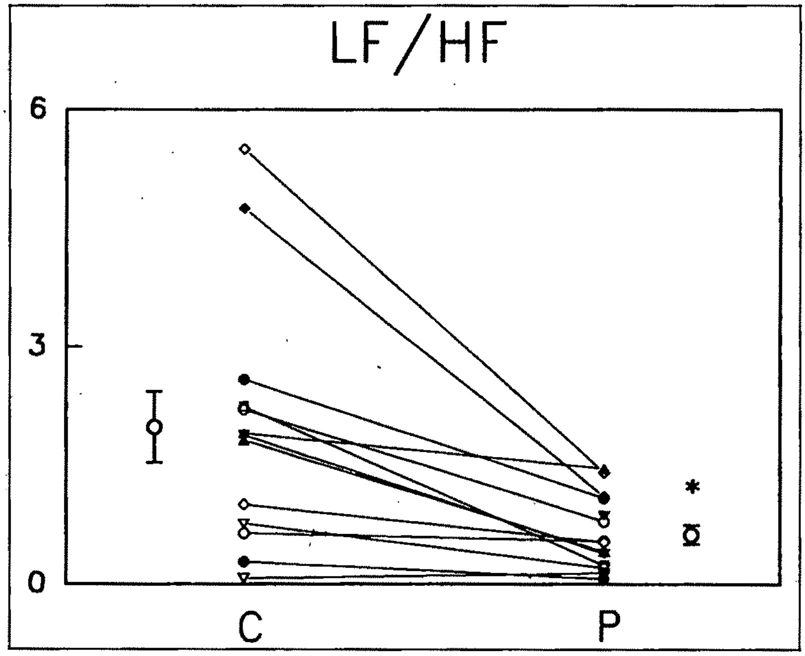

FIGURE 3. Effects of propafenone on low-/high-frequency (LF/HF) ratio in individual patients. C = control; P = after propafenone; *p <0.05.

whereas RR variance was slightly but not significantly reduced. During tilt, the low-frequency component increased from 27 ± 5 to 54 ± 7 nu, whereas the high-frequency component decreased from 48 ± 6 to 33 ± 7 nu. As a consequence, the low-/high-frequency ratio increased from 0.80 ± 0.28 to 4 ± 1. All these values were significantly different from those observed during tilt before drug administration.

DISCUSSION

This study indicates that propafenone administration is associated with significant changes in spectral indexes of RR variability, which are consistent with an antiadrenergic effect of the drug. These results appear important in regard to the methodology used to evaluate sympathovagal interaction, as well as to the possible clinical relevance of the β-adrenergic receptor blockade properties of this drug.

Assessment of sympathovagal interaction by spectral analysis of RR variability: In the present study, spectral analysis of RR variability was used to evaluate sympathovagal interaction. This approach,[16,18,19] by providing indexes of parasympathetic (high-frequency component) and sympathetic (low-frequency component) modulation of the heart period, provides adequate information with which to evaluate alterations in neural

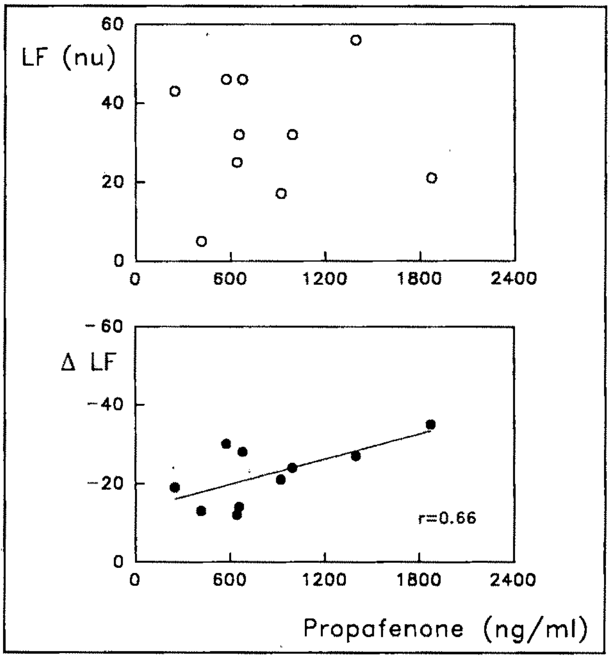

FIGURE 4. *Top,* relation between plasma concentrations of propafenone and amplitude of low-frequency (LF) component after drug administration. *Bottom,* relation between plasma concentrations of propafenone and changes in low-frequency component induced by drug.

control mechanisms in different conditions such as myocardial infarction[20,21] and hypertension.[22] Two features of our methodology need to be considered for their relevance to the observed results. We expressed the amplitude of spectral components in normalized rather than absolute units to facilitate the appraisal of the effects of propafenone on spectral components in terms of reciprocal changes, as frequently observed in sympathovagal balance. Furthermore, the use of normalized units makes low- and high-frequency components less dependent on the absolute values and changes in RR variance induced by various interventions. After propafenone administration, we observed a marked reduction in RR variance, a finding that if considered by itself would have led to a different conclusion[23] than that which we ultimately reached. The antiadrenergic effect of propafenone was confirmed when considering the drug-induced changes in the low-/high-frequency ratio; with this parameter, similar information can be obtained by evaluating spectral components in either absolute or normalized units.

Whereas the high-frequency oscillations have been considered a marker of vagal modulation since the initial observation,[24,25] interpretation of the low-frequency component as an index of sympathetic activation (which was controversial in the past)[24] appears now to be confirmed.[16] In this study, spectral analysis of RR variability was performed by using an autoregressive modelling technique[16,18] that at variance with the fast Fourier transform algorithm may operate efficiently in shorter series of events. This was the case in some patients where a tachogram of 150 RR intervals only could be considered for the presence of frequent ventricular premature beats.

Effects of propafenone on RR variability: Propafenone did not modify the duration of the RR interval during resting conditions. This negative finding, which is consistent with previous observations,[26] is related, in our

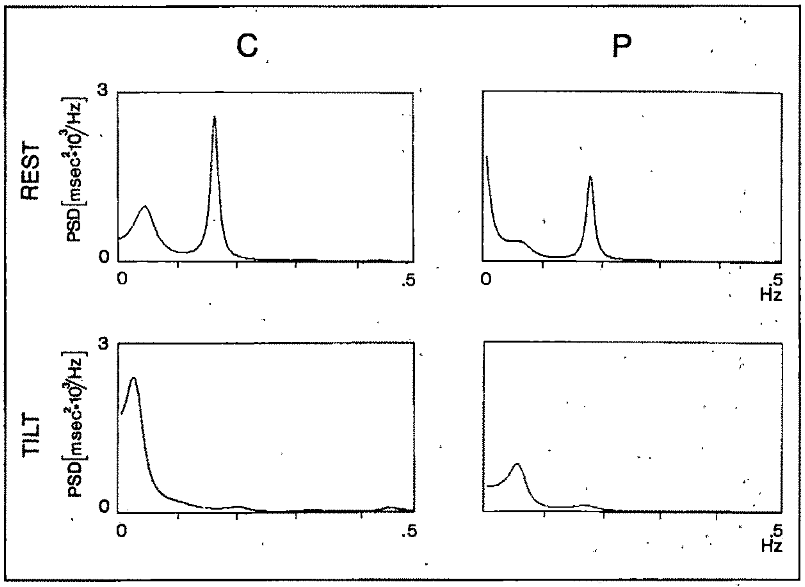

FIGURE 5. Representative example of RR variability in patient before *(left)* and after *(right)* propafenone in resting conditions *(top)* and during tilt *(bottom)*. Notice reduction in low-frequency component response to tilt after drug administration. C = control; P = after propafenone; PSD = power spectrum density.

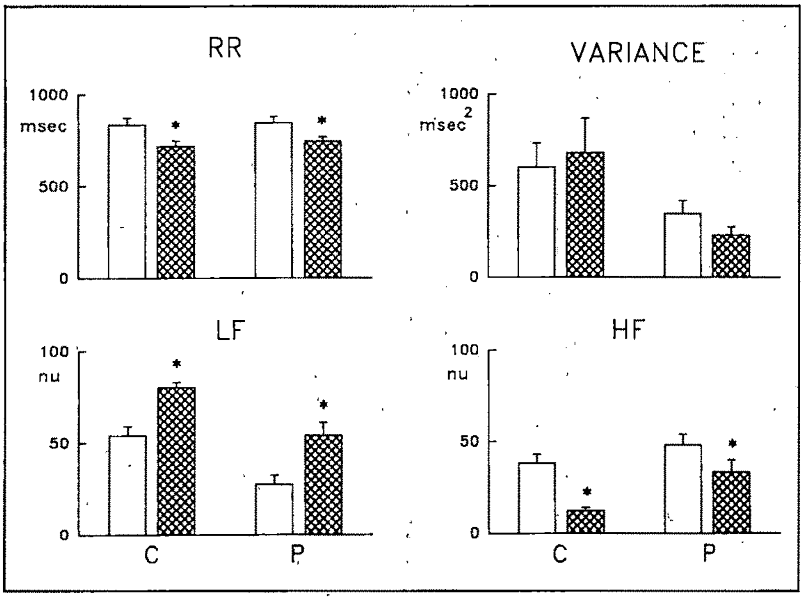

FIGURE 6. Effects of tilt *(filled bars)* on RR variability before and after propafenone. Abbreviations as in Figure 2. *p <0.05.

opinion, to the fact that resting heart rate is mediated predominantly by vagal tone. However, we noticed a slight reduction in the amount of sinus tachycardia induced by tilt, an effect that is in keeping with the description of a blunting of the increase in heart rate at peak exercise and during isoproterenol infusion in normal subjects.[27]

The effects of propafenone on total RR variance deserve a few considerations. RR variance reflects the spontaneous fluctuations of the RR interval, which are the result of a complex interaction between sinus node pacemaker properties and sympathetic and vagal neural regulatory activities. Changes in any of these components may induce similar modifications in the magnitude of RR variability and its measures. Thus, it is likely that multiple and varied mechanisms may contribute to determine the reduction in RR variability observed in distinct clinical conditions such as myocardial infarction,[10,11,28] diabetes,[16] congestive heart failure[29] and heart transplant.[30] In this study, by using spectral techniques, we were able to demonstrate that propafenone determined a significant reduction in the low-frequency component at rest and in response to sympathetic stimulation induced by passive tilt. A significant increase in the high-frequency component was also observed; as a result the low-/high-frequency ratio markedly decreased. All these changes were consistent with a shift of sympathovagal balance toward a parasympathetic predominance. The observed changes in spectral components were similar to those described after β-adrenergic receptor blockade.[16,19,31,32] Furthermore, the correlation between the changes in the low-frequency component induced by propafenone and its serum levels indicates that the antiadrenergic effect is more evident at higher drug concentrations.

Clinical relevance of the β-blocking effect of propafenone: Since the Cardiac Arrhythmia Suppression Trial,[1] β blockers remain the only pharmacologic intervention that has been shown to reduce sudden cardiac death. A complex antiarrhythmic drug such as propafenone, by combining different electrophysiologic effects, may have beneficial results in some patients as a consequence of multiple actions at different levels.[2] The attenuation of heart rate responses to sympathetic stimulation or the reduction in cycle length of ventricular tachycardia determined by the β-blocking properties may influence the kinetics of the use-dependent effects of the drug by prolonging the duration of the intervals between excitations. Thus, in areas of mildly depressed conduction and excitability, as may occur in patients after myocardial infarction, these rate effects may prevent the initiation of reentrant rhythms secondary to the presence of areas of unidirectional block induced by sodium channel blockade.

In conclusion, the appraisal of the multifactorial mechanisms involved in sudden cardiac death,[33] as well as the suggestion that some proarrhythmic effects of antiarrhythmic agents may be suppressed by concomitant administration of β blockers,[34] constitutes a new framework within which the specific characteristics of each antiarrhythmic drug should be reevaluated.

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Stress Response Pattern in Obesity and Systemic Hypertension

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Under resting conditions obese hypertensive patients have been described as having a greater cardiac output and lower total peripheral resistance than lean hypertensive patients. To evaluate the hemodynamic patterns under stress conditions, we determined the hemodynamic response to mental stress (first study) and during isometric exercise (second study) in hypertensive patients with a body mass index >27 kg/m^2 (obese) and <27 kg/m^2 (lean). The cohort exposed to mental stress comprised 54 white male patients (30 were lean, 24 were obese) with untreated stage I or II essential hypertension according to the World Health Organization. Obese subjects responded with a higher increase in total peripheral resistance ($p < 0.02$) and lower increases in heart rate ($p < 0.01$), cardiac output ($p < 0.01$) and stroke volume ($p < 0.02$) when compared with their lean counterparts. This was independent of any differences in chemical or baseline hemodynamic characteristics at rest. The cohort exposed to isometric stress consisted of 57 patients (30 were lean, 27 were obese) with World Health Organization stage I or II essential hypertension. Obese subjects responded with exaggerated increases in systolic ($p < 0.04$) and diastolic ($p < 0.01$) pressures, and heart rate ($p < 0.04$) when compared with lean patients. Body mass index emerged as an independent determinant of the increase in systolic ($r = 0.03$) and diastolic ($r = 0.01$) pressure as well as of heart rate ($r = 0.03$). These results indicate that obese hypertensive patients respond to (1) mental stress with vasoconstriction instead of the expected vasodilation, and to (2) isometric stress with an exaggerated increase in arterial pressure. These findings argue against the concept that obesity would be prone to mitigate the effects of hypertensive vascular disease.

(Am J Cardiol 1992;70:1035–1039)

Numerous studies have shown a correlation between obesity and systemic hypertension.[1-3] Hemodynamically, obese hypertensives are characterized by an elevated cardiac output and expanded intravascular volume.[4,5] At the same time, vascular resistance was observed to be lower in obese than in lean hypertensive patients with similar arterial blood pressure (BP) at rest.[4,5] As a consequence of diminished vascular resistance, patients with obesity hypertension have been considered to be hemodynamically "younger" than lean subjects and to have a lower risk of hypertensive vascular disease.[6] Indeed, several large-scale follow-up studies[7,8] reported an attenuated risk for cardiovascular mortality and morbidity among patients in whom arterial hypertension coexisted with obesity. However, other prospective studies of similar size[9,10] contradicted these results and failed to confirm that obese hypertensive patients had a lower risk for cardiovascular complications than lean hypertensive subjects. Because of the controversy surrounding effects of obesity on cardiovascular risks in hypertension, the present study was designed in order to assess the pattern of response to stress in lean and obese hypertensive patients.

METHODS

Study population I: Fifty-four white male civil servants (mean age 45 ± 9 years) with mild to moderate essential hypertension (World Health Organization stage I or II) were enrolled in this study. They were screened for high BP at their work site in Bonn, in 1989/1990, had never received antihypertensive therapy in the past, and remained untreated throughout the study. Only subjects with elevated diastolic BP (>90 mm Hg) on at least 3 of 4 initial casual pressure readings were included in the study. No patient had evidence of secondary hypertension according to routine workup including digital subtraction angiogram of the renal arteries and hormone analysis. Electrocardiograms revealed no abnormalities, and echocardiogram showed no decrease in ejection fraction in all patients. Body mass index (weight/height^2) served as a measure of the degree of obesity. Patients with a body mass index >27 kg/m^2 were considered obese, and those with a body mass index below that level were said to be lean. This cutoff point corresponds to the obesity definition of large-scale epidemiologic studies: In the National Health and Nutrition Examination Survey 1976–1980,[11] a body mass index exceeding the 85th percentile (overweight = excess of body mass index ≥27.8 kg/m^2 in men) was considered to be an appropriate cutoff point.[12] According to the Metropolitan Life Insurance tables,[12,13] a body weight 20% above desirable weight

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TABLE I Clinical Characteristics of Study Population I

	BMI <27 kg/m^2 (n = 30)	BMI >27 kg/m^2 (n = 24)	p Value
Age (year)	46 ± 8	45 ± 9	NS
Men	30	24	—
White	30	24	—
Height (cm)	178 ± 5	176 ± 7	NS
Weight (kg)	77 ± 6	90 ± 10	<0.001
BMI (kg/m^2)	24 ± 1.8	29 ± 1.6	<0.001
Casual blood pressure			
Systolic (mm Hg)	144 ± 11	149 ± 16	NS
Diastolic (mm Hg)	98 ± 9	100 ± 11	NS
Resting blood pressure			
Systolic (mm Hg)	137 ± 11	141 ± 17	NS
Diastolic (mm Hg)	89 ± 7	93 ± 12	NS
Peak blood pressure			
Systolic (mm Hg)	163 ± 21	162 ± 20	NS
Diastolic (mm Hg)	100 ± 9	107 ± 13	<0.02

BMI = body mass index; NS = not significant.

corresponded to a body mass index of >27.2 kg/m^2 for men. The protocol for the study was approved by our clinical investigation committee, and informed consent was obtained from each participant.

Hemodynamic measurements during mental stress test (study I): All psychophysiologic examinations were performed between 9 and 10 A.M. after a light breakfast without tea or coffee. Patients of study population I were seated in a semirecumbent position in a reclining chair, and our recording devices were attached. Patients were left alone in a sound-protected room with an ambient temperature of about 21°C. All data were monitored and recorded in an adjacent room. After a period of 20 to 30 minutes for attachment of probes, baseline hemodynamic variables were determined at rest and subsequently during the stress period. BP was measured every minute with a 2-probe ultrasonic device for separate detection of systolic and diastolic BP.[14] Heart rate was continuously assessed from an electrocardiogram (lead II). Stroke volume was assessed continuously by impedance cardiography (IFM model 400, Minnesota impedance cardiograph, Fa. Diefenbach, Frankfurt, Germany), a method repeatedly validated and used by various groups.[14,15] Cardiac output was calculated from stroke volume and heart rate, and total peripheral resistance was derived from mean arterial pressure and cardiac output.

Mental stress consisted of the continuous performance of simple arithmetic exercises (adding 1- and 2-digit numbers played over headphones at a speed of 1 number every 2 seconds for 3 minutes). The subjects were instructed to work as accurately as possible. Simultaneously they were distracted by the counterrhythmic beat of a metronome.

Study group II: A total of 57 male patients (mean age 45 ± 12 years) with mild to moderate essential hypertension (World Health Organization class I or II), all recruited from the outpatient hypertension clinic in New Orleans in 1989, formed the study population II (44 white and 13 black patients). All patients enrolled in the study protocol had repeated diastolic BP >90 mm Hg when measured in the clinic. All patients had known their diagnosis for ≥ 3 months and had received no medication for ≥ 4 weeks before study onset. Secondary causes of hypertension and target organ damage were excluded by clinical laboratory investigation.[16] Our clinical investigation committee approved the study protocol, and informed consent was obtained from each patient before the study. Electrocardiograms revealed no abnormalities, and an echocardiogram showed no decrease in ejection fraction in all patients.

Hemodynamic measurements during isometric stress test (study II): Study II was performed early in the morning. Hemodynamic assessment was performed 1 hour after catheterization of the brachial artery[16] while patients were at complete rest. The hemodynamic measurements were performed by way of a catheter with its tip in the subclavian artery or aortic arch. Cardiac output was measured in triplicate using the indocyanine green dye dilution technique, and heart rate was determined from the standard electrocardiogram. Stroke volume, total peripheral resistance, and all hemodynamic indexes were derived by standard formulas.[16] Mean arterial pressure was obtained by electrical integration. Before the onset of hemodynamic evaluation, the maximal strength of each subject's isometric handgrip was determined. Patients were then instructed to perform isometric handgrip at one third of the maximal contraction for ≥ 3 minutes and to breathe normally in order to avoid any Valsalva maneuver. Hemodynamic measurement took place at baseline before isometric handgrip and after the third minute of continuous isometric stress.

Statistical analysis: For statistical analysis of the mental arithmetic test, mean values were averaged for the last 5 minutes of the period before stress and for the second and third minutes of mental arithmetic. For the isometric exercise, the average of 3 resting measurements and the stress values measured in the third minute were entered for statistical analysis. One-way analysis of variance and Bonferoni's correction equation were used to evaluate any significant differences in the hemodynamic responses to stress between lean and obese hypertensive subjects. To exclude any potential impact of age and baseline hemodynamics on the cardiovascular reaction to stress, the general linear regression model was applied. Pearson correlation coefficients were computed where indicated. Unless otherwise specified, data are given as mean ± 1 standard deviation. All statistical analyses were made on an IBM 308-1 computer by using SAS programs.[17]

RESULTS

Mental stress (study I): Clinical characteristics of the lean versus the obese subgroup of study population I are listed in Table I. During mental stress, obese patients were characterized by a slightly more pronounced increase in diastolic BP (15 ± 5 vs 11 ± 4 mm Hg; $p < 0.10$) and a higher peak diastolic BP during stress (107 ± 13 vs 100 ± 9 mm Hg; $p < 0.02$) when compared with lean counterparts.

The hemodynamic profile in lean hypertensive patients during mental stress was characterized by a decrease in total peripheral resistance. In contrast, obese hypertensive patients showed an increase in total peripheral resistance ($p < 0.03$) (Figure 1). The increase in total peripheral resistance during mental stress correlated with body mass index in all patients ($r = 0.42$, $p < 0.01$; Figure 2). In lean hypertensive patients, pronounced increases in cardiac output and, to a lesser extent, in heart rate and stroke volume were observed, whereas obese hypertensive patients exhibited a blunted increase in cardiac output and heart rate ($p < 0.003$ and $p < 0.01$, respectively; Figure 1). Changes in stroke volume differed between the obese and lean hypertensive groups ($p < 0.012$), whereas changes in mean arterial pressure did not (Figure 1).

To rule out any bias caused by differences in the clinical characteristics between lean and obese hypertensive patients (such as age, casual BP, and BP at rest [Table I]), we analyzed our data with the linear regression model. Body mass index was still found to correlate with increased heart rate ($p = 0.02$), cardiac output

TABLE II Clinical Characteristics of Study Population II

	BMI <27 kg/m^2 (n = 30)	BMI >27 kg/m^2 (n = 27)	p Value
Age (year)	48 ± 12	43 ± 11	0.07
Men	30	27	—
White:black	23:4	21:9	NS
Height (cm)	175 ± 7	173 ± 7	NS
Weight (kg)	77 ± 10	91 ± 10	<0.0001
BMI (kg/m^2)	24.8 ± 2.0	30.6 ± 2.6	<0.0001
Casual blood pressure			
Systolic (mm Hg)	168 ± 24	165 ± 19	NS
Diastolic (mm Hg)	100 ± 13	101 ± 11	NS
Resting blood pressure			
Systolic (mm Hg)	164 ± 25	156 ± 17	0.15
Diastolic (mm Hg)	92 ± 12	94 ± 11	NS
Peak blood pressure			
Systolic (mm Hg)	190 ± 27	192 ± 27	NS
Diastolic (mm Hg)	106± 12	114 ± 14	<0.10

BMI = body mass index; NS = not significant.

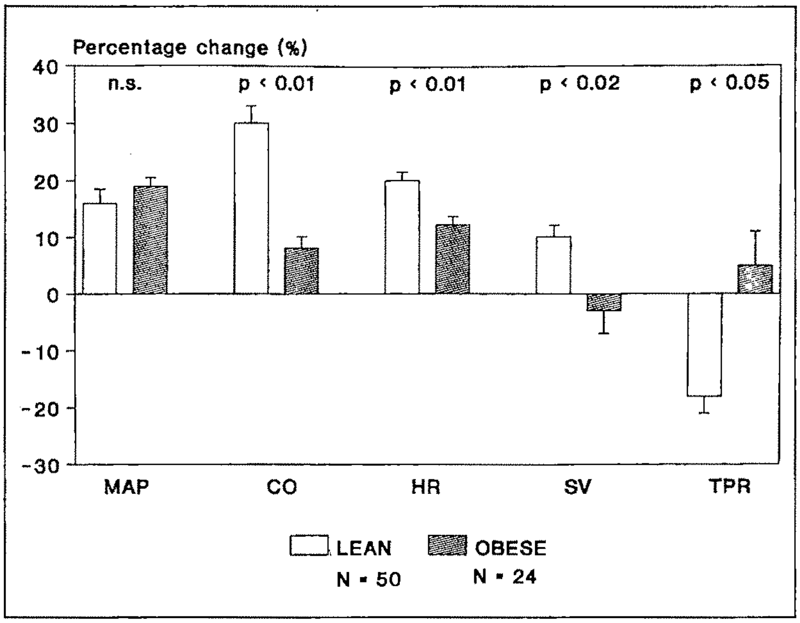

FIGURE 1. Hemodynamic changes during mental stress in obese (body mass index >27 kg/m^2) and lean (body mass index <27 kg/m^2) hypertensive patients (study I). CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; n.s. = not significant; SV = stroke volume; TPR = total peripheral resistance.

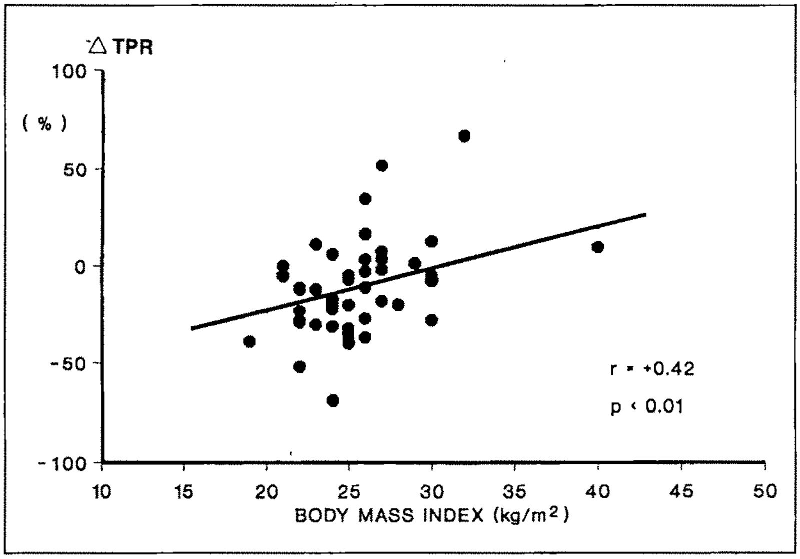

FIGURE 2. Correlation between changes in total peripheral resistance (TPR) and body mass index (study I).

(p = 0.03), stroke volume (p = 0.09), diastolic BP (p = 0.09) and total peripheral resistance (p = 0.001) independent of age or casual or resting BP.

Thus, in obese hypertensives, mental stress caused an exaggerated increase in total peripheral resistance and, conversely, an attenuated increase in cardiac output resulting in an elevated peak diastolic pressure.

Isometric stress (study II): Clinical characteristics of the lean and obese hypertensive groups in study population II are found in Table II. Isometric stress induced a more pronounced increase in systolic (36 ± 16 vs 26 ± 15 mm Hg, $p < 0.04$) and diastolic (20 ± 10 vs 13 ± 9 mm Hg, $p < 0.01$) BP in obese hypertensive patients than it did in the lean group. The increase in diastolic BP during isometric exercise correlated with body mass index in all patients ($r = 0.30$, $p < 0.05$; Figure 3).

TABLE III Hemodynamic Pattern of Response to Mental and Isometric Stress (studies I and II, respectively) in Lean and Obese Hypertensive Patients

	Mental Stress (study I)		Isometric Stress (study II)	
	ΔDBP	ΔTPR	ΔDBP	ΔTPR
Physiologic response	↑	↓	↑	↑
Lean hypertensives	↑	↓	↑	↑
Obese hypertensives	↑ ↑	↑ ↑	↑ ↑ ↑	↑ ↑

ΔDBP = change in diastolic blood pressure; ΔTPR = change in total peripheral resistance; ↑ = slight increase (mild); ↑ ↑ = moderate increase; ↑ ↑ ↑ = marked increase.

During isometric stress, obese hypertensives were characterized by a significantly greater increase in total peripheral resistance than their lean counterparts ($p < 0.03$) (Figure 4). The latter finding corresponds to the exaggerated increase in mean arterial pressure in obese hypertensive patients in response to isometric exercise ($p < 0.02$). No significant differences between the 2 groups were found in cardiac output and stroke volume. A higher increase in heart rate ($p < 0.04$) was observed in lean than in the obese hypertensives (Figure 4).

Again, the linear regression model was applied to the data of study population II to eliminate any bias caused by differences in resting or casual BP, age, race or sex. Body mass index still remained a significant determinant of the increases in systolic (p = 0.028) and diastolic (p = 0.009) BP, and heart rate (p = 0.026). Thus, the

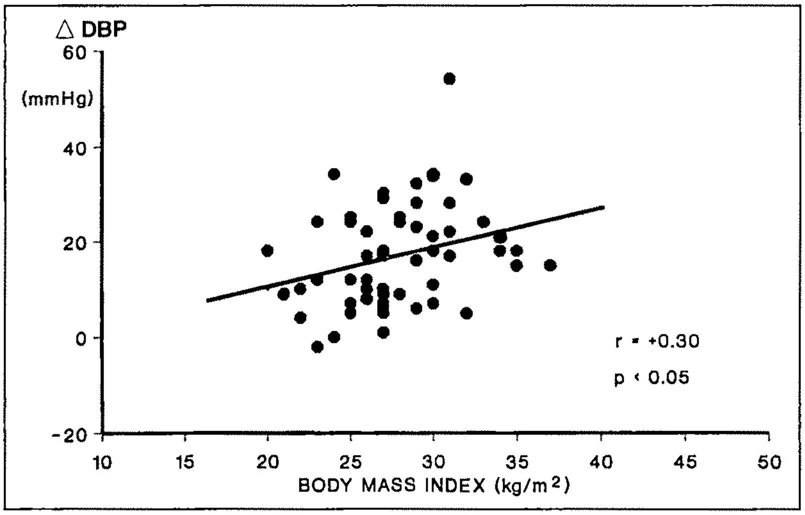

FIGURE 3. Correlation between increase in diastolic pressure (DBP) and body mass index (study II).

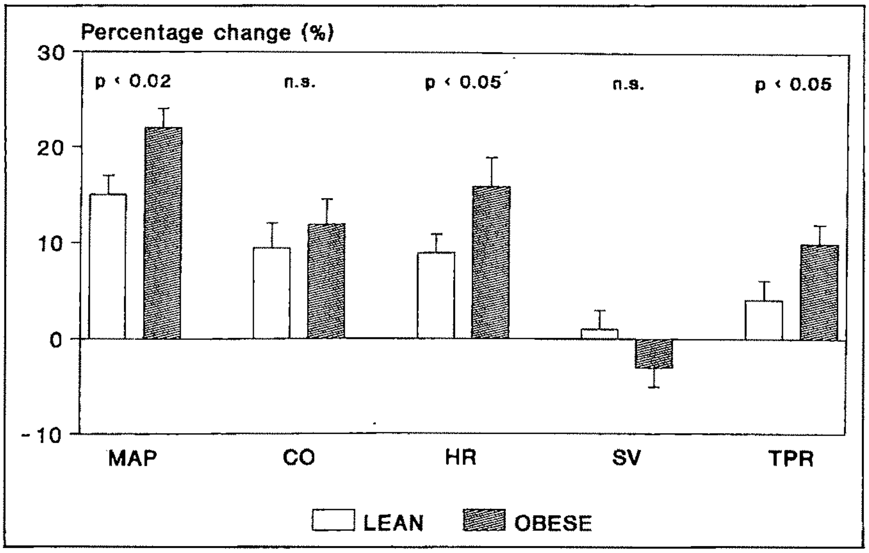

FIGURE 4. Hemodynamic changes during isometric stress in obese (body mass index >27 kg/m²) and lean (body mass index <27 kg/m²) hypertensive patients (study II). Abbreviations as in Figure 1.

response to isometric stress in obese hypertensives appeared to be characterized by an exaggerated increase caused by marked vasoconstriction.

DISCUSSION

Mental stress and isometric stress have been shown to increase BP in normotensive as well as hypertensive subjects.[18] However, the mechanisms of this pressure elevation have not been found to be identical for both stressors.[19,20] With mental stress, the increase in BP is accompanied by an increase in cardiac output and heart rate and a decrease in total peripheral resistance. These hemodynamic changes seem to result predominantly from the release of epinephrine.[19] In contrast, with isometric stress, the hemodynamic pattern is determined by the release of both epinephrine and norepinephrine, leading to an increase in heart rate and cardiac output and no change or a slight increase in total peripheral resistance.[21-23]

In the present study, obese hypertensive patients responded to mental stress with an increase in cardiac output that was far less pronounced than the response seen in lean hypertensives. In addition, stroke volume decreased and, more importantly, total peripheral resistance increased during mental stress in obese hypertensives. This hemodynamic response pattern was independent of age, sex, and level of BP as determined by a multiple regression analysis.

In contrast, with isometric stress the response pattern of obese hypertensive patients was qualitatively similar to that of lean subjects. However, BP increased considerably more in obese patients, and this increase was mediated by an excessive increase in total peripheral resistance. Thus, obesity seems to modify the hemodynamic pattern of response to mental and isometric stress: With mental stress, vasoconstriction rather than vasodilation is seen, whereas with isometric stress, the response in BP becomes more exaggerated in obese hypertensive than in lean hypertensive patients (Table III).

The present study was not designed to settle the controversy brought about by epidemiologic findings, i.e., whether obesity has a beneficial effect on cardiovascular risk factors in patients with essential hypertension. Nevertheless, our data indicate that under conditions of mental or isometric stress the hemodynamic pattern is less favorable in obese than in lean hypertensive patients. Clearly, however, the prognostic implications of this different response pattern remain to be determined.

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Transesophageal Echocardiographic Monitoring of Percutaneous Mitral Balloon Valvulotomy

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This study was designed to evaluate the usefulness of performing transesophageal echocardiography (TEE) during percutaneous mitral balloon valvulotomy (PMBV). TEE was performed in 35 consecutive patients with symptomatic severe mitral stenosis during PMBV (group A). Another group of 27 patients with mitral stenosis who underwent PMBV without TEE was used for comparison (group B). TEE was most helpful in guiding transseptal puncture, aiding in proper positioning of the balloon during the dilatation procedure and enabling early detection of complications. The results show that PMBV when aided by TEE has a tendency to decrease the frequency of significant mitral regurgitation without compromising the final mitral valve area. TEE decreased the x-ray exposure time and was well-tolerated. Thus, TEE provides information that makes this interventional catheterization procedure safer and easier to perform.

(Am J Cardiol 1992;70:1040–1044)

Percutaneous mitral balloon valvulotomy (PMBV) has been established as a nonsurgical, alternative therapy for mitral stenosis.[1-3] Two-dimensional echocardiography is an invaluable adjunct for patient selection.[4,5] Furthermore, 2-dimensional and Doppler echocardiography can be readily performed after PMBV to assess results. Transthoracic and transesophageal echocardiography (TEE) have also been used for guiding the transseptal needle across the atrial septum.[6,7] Scattered reports of the usefulness of transthoracic echocardiography and TEE during PMBV have been published.[8,9] TEE provides excellent images of the atrial chambers, interatrial septum and mitral morphology without interfering with catheterization techniques.[10] This study evaluates the usefulness of TEE during PMBV.

METHODS

Study patients: From March 1990 to April 1991, PMBV was performed in 35 consecutive patients (27 women and 8 men, mean age 53 ± 11 years, range 26 to 65) with symptomatic mitral stenosis (group A). There were 15 patients in sinus rhythm and 20 in atrial fibrillation. Five patients were in New York Heart Association functional class IV, 16 in class III, and 14 in class II. Four patients had undergone closed mitral commissurotomy previously. Informed consent was obtained from all patients. Patients with left atrial thrombus or severe mitral regurgitation detected by transthoracic echocardiography or TEE were excluded from the study.

Initially, TEE in PMBV was not routine in our institution, but this policy changed when TEE became available. To better determine the usefulness of TEE during PMBV, 27 patients (22 women and 5 men, mean age 49 ± 12 years, range 25 to 60) without transesophageal echocardiographically monitored PMBV were used for comparison (group B). Fourteen patients were in atrial fibrillation, and 13 were in sinus rhythm. Four patients were in functional class IV, 14 in class III, and 9 in class II.

Seventeen patients (11 in group A and 6 in group B) had concomitant, mild mitral regurgitation.

Percutaneous balloon mitral valvulotomy: All patients underwent diagnostic left and right heart catheterization before PMBV. Inoue balloon was used for PMBV in all patients. Transseptal catheterization was performed with an 8Fr Mullins transseptal dilator and a modified Brockenbrough needle. After entry in the left atrium, 10,000 units of heparin were administered. Simultaneous pressure tracings of the left atrium and ventricle were recorded. Cardiac output was measured with

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the thermodilution method, and mitral valve area was calculated with the Gorlin formula. A stainless steel guide wire was advanced in the left atrium and used to place the Inoue balloon catheter in the left atrium. After entering the left atrium, the balloon was passed through the mitral orifice into the left ventricle with continuous fluoroscopic and echocardiographic guidance. Balloon inflations were then performed until hemodynamic and echocardiographic measurements were satisfactory or complications appeared. Mitral regurgitation was evaluated with cine left ventriculography and its severity was graded by the Seller's classification. Right-sided heart oximetry was performed to evaluate interatrial shunting.

Transesophageal echocardiography: TEE was performed during PMBV using a commercially available Toshiba SSH-160 echocardiograph machine interfaced with a 5-MHz transducer, mounted on a flexible endoscope. After administering 3 to 8 mg of intravenous diazepam and 25 to 75 mg of intravenous meperidine, and topically anesthetizing the posterior pharynx with 10% xylocaine spray, the transesophageal probe was introduced in the esophagus and positioned posterior to the left atrium. In each patient from group A, the site of the interatrial septal puncture was chosen on the basis of echocardiographic findings. The probe was aimed to enable visualization of the maximal length of the atrial septum. Special emphasis was given to visualizing the relation between the atrial septum and aorta to ensure that the needle tip was not in the vicinity of the aorta. After the transseptal needle and surrounding sheath appeared in the right atrium, they were directed under 2-dimensional echocardiography to the thinnest portion of the atrial septum (fossa ovalis). To ensure proper positioning, the atrial septum was expected to bulge toward the left atrium if some pressure was applied on the transseptal catheter (tent sign) (Figure 1). After the needle had crossed the atrial septum, it was snapped back to its original position (Figure 2). Contrast echocardiography performed during flushing of the needle confirmed its location in the left atrium after the puncture. After entering the left atrium, the balloon was guided through the stenotic mitral valve orifice assisted by a combination of echocardiographic and fluoroscopic imaging. Before inflation, adequate positioning of the balloon was routinely assessed by TEE. Before, during and after balloon inflations, presence and degree of mitral regurgitation was semiquantitatively assessed by transesophageal color Doppler echocardiography. Furthermore, maximal mitral leaflet separation (i.e., maximal distance during diastole between the 2 tips of mitral valve leaflets) was measured before and after each balloon inflation in the transesophageal echocardiographic 4-chamber view. Finally, after PMBV, the presence and size of interatrial shunting was assessed.

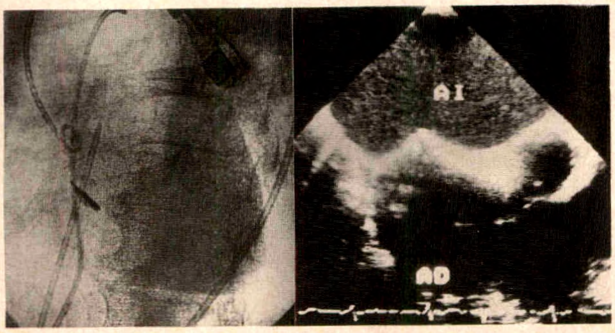

FIGURE 1. Transesophageal 2-dimensional echocardiography. Triangular configuration of atrial septum (tent sign) caused by transseptal needle can be seen. AD = right atrium; AI = left atrium.

All patients from group B underwent TEE 3 to 6 months after PMBV to assess results.

Data and statistical analysis: Student's *t* and chi-square tests were used for comparing hemodynamic parameters and clinical results. The examined factors were age, sex, cardiac rhythm, history of commissurotomy, echocardiographic subgrouping, mitral valve area before and after PMBV, balloon diameter normalized to body surface area, degree of mitral regurgitation according to left ventriculography, procedure time and x-ray exposure. A p value <0.05 was considered significant.

RESULTS

Clinical profile (including sex, age, functional class, cardiac rhythm and previous commissurotomy), echocardiographic score (group A: 7.15 ± 2.70; and group B: 7.5 ± 3.0) and mitral valve area before PMBV (group A: 0.95 ± 0.22 cm^2; and group B: 0.96 ± 0.78 cm^2) were similar in both groups.

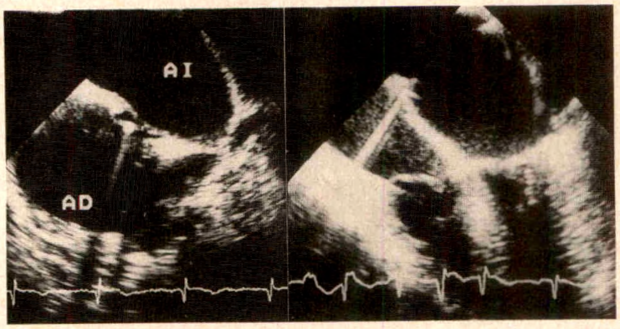

FIGURE 2. Transesophageal 2-dimensional echocardiography; 4-chamber view. Transseptal needle had crossed atrial septum. AD = right atrium; AI = left atrium.

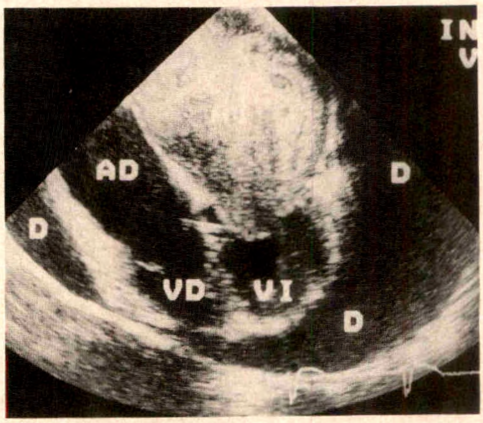

FIGURE 3. Transesophageal 2-dimensional echocardiography; 4-chamber view demonstrating mitral stenosis with spontaneous contrast and concomitant severe pericardial effusion (D). AD = right atrium; AI = left atrium; VD = right ventricle; VI = left ventricle.

In each patient from group A, the location of the fossa ovalis and its relation to the needle and transseptal catheter could be clearly visualized. In all patients in group A, atrial septal puncture was performed through the fossa ovalis. "Tent sign," the triangular configuration of the atrial septum after applying some pressure on the transseptal catheter, was visualized in all patients. TEE was particularly useful in 4 patients with an aneurysmatic left atrium, in 1 with aortic root dilation and in 1 with concomitant severe pericardial effusion (Figure 3). In these patients, the anatomic landmarks were markedly distorted. A small, acquired atrial septal defect with left-to-right shunting was visualized in all patients from group A at the end of PMBV (Figure 4). However, a significant oxygen step-up was not present in the right heart in any patient. The mean diameter of the atrial septal defect measured by TEE was 1.5 ± 1.0 mm. The mean velocity of left-to-right shunting flow measured by Doppler was 0.90 ± 0.30 m/s.

In group B, puncture of the aortic root was detected in 2 patients; the needle was immediately withdrawn, and the left atrium was entered in another attempt without complications. One patient had puncture of the right atrial wall, which led to severe pericardial effusion needing surgical intervention. In 4 patients from group B, a left-to-right shunt was detected 4 to 6 months after PMBV (1 in the fossa ovalis, and 3 in the posterior muscular portion of the atrial septum; Figure 5). No such defect was detected in patients from group A. The mean diameter of the defect in the aforementioned 4

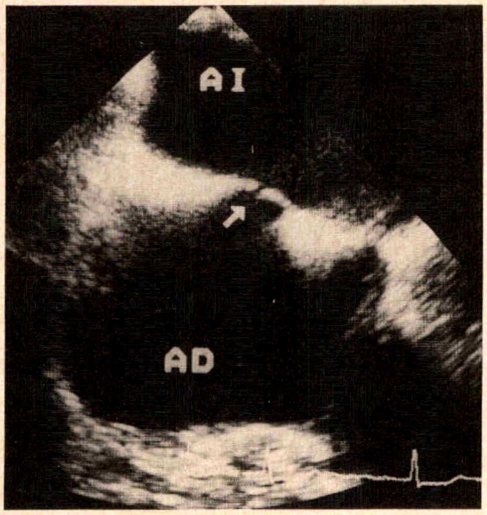

FIGURE 4. Transesophageal 2-dimensional echocardiography performed during mitral valvulotomy procedure. Small atrial septal defect in fossa ovalis can be seen *(arrow)*. AD = right atrium; AI = left atrium.

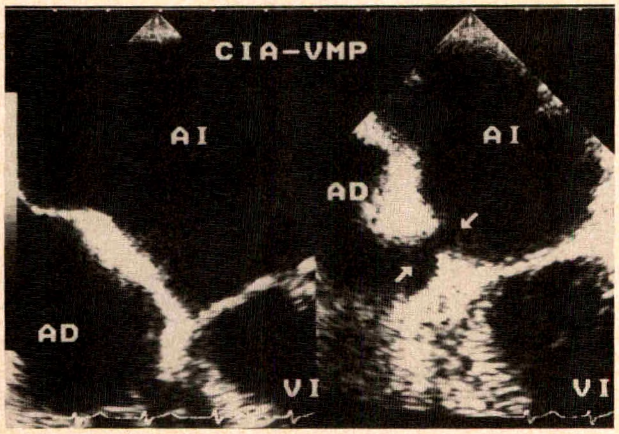

FIGURE 5. Transesophageal 2-dimensional echocardiography performed during mitral valvulotomy procedure. Posterior muscular atrial septal defect *(arrows)* is visualized. Abbreviations as in Figure 3.

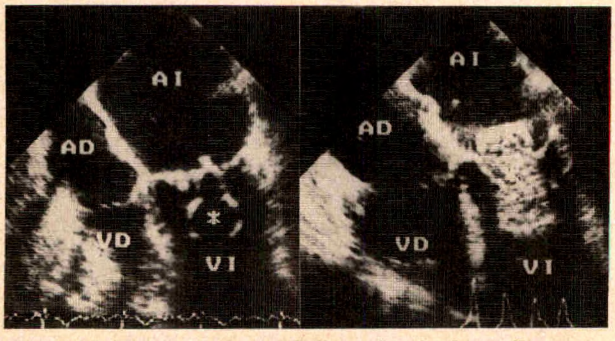

FIGURE 6. Transesophageal 2-dimensional echocardiography; 4-chamber view. *Left,* partially inflated balloon *(asterisk)*. *Right,* totally inflated balloon at mitral valve orifice. Abbreviations as in Figure 3.

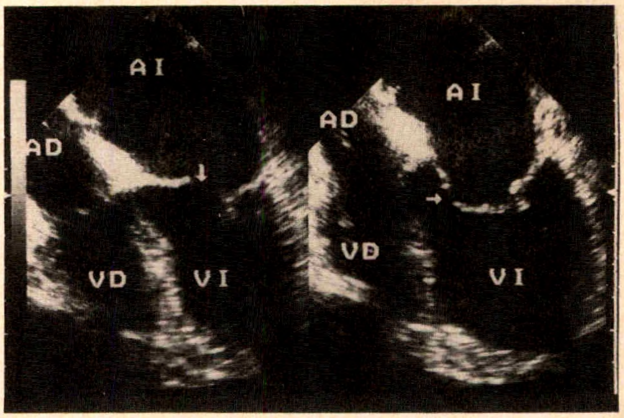

FIGURE 7. Transesophageal 2-dimensional echocardiography; 4-chamber view; systolic *(left)* and diastolic *(right)* frames demonstrating rupture of anterior mitral leaflet *(arrows)*. Abbreviations as in Figure 3.

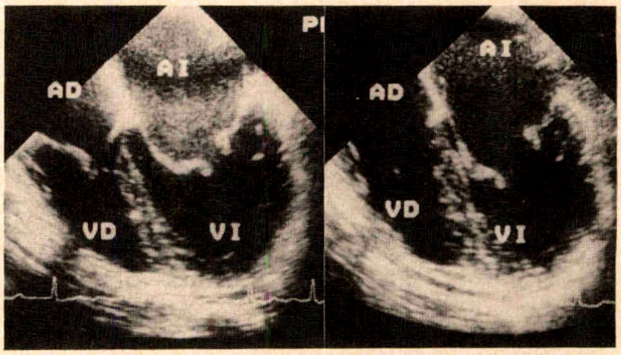

FIGURE 8. Transesophageal 2-dimensional echocardiography; 4-chamber view; diastolic frame. *Left,* mitral stenosis with spontaneous contrast in left atrium (AI). Maximal mitral leaflet separation before dilation. *Right,* mitral stenosis after valvulotomy. Amount of spontaneous contrast within left atrium decreased compared with before valvulotomy, and maximal mitral leaflet separation increased. Other abbreviations as in Figure 3.

patients was 2.5 ± 1.0 mm, and the mean velocity was 0.80 ± 0.20 m/s. Oximetry had demonstrated left-to-right shunts of pulmonary-to-systemic flow ratio of 1.3:1 and 1.4:1 in 2 of these patients with muscular atrial septal defect. No left-to-right shunts were found in the remaining 23 patients from group B by oximetry after PMBV.

After transseptal puncture, a wire was advanced in the left atrium, the needle was removed, and the Inoue balloon was positioned in the left atrium. During manipulation of the balloon, TEE could detect its exact location, and helped in redirecting the balloon when it reached the left atrial appendage and the ceiling and lateral wall of the left atrium. After entering the left ventricle, proper positioning of the balloon before inflation was correctly assessed by TEE in all patients. Visualization of the balloon continued throughout the balloon inflation (Figure 6).

Patients from group A had a larger number of balloon inflations (58 inflations: 1 in 19 patients, 2 in 9 patients and 3 in 7 patients; mean: 1.6 ± 0.8 inflation/patient) than did those from group B (32 inflations: 1 in 22 patients and 2 in 5 patients; mean 1.1 ± 0.3 inflation/patient) ($p = 0.002$). Despite this difference in the number of balloon inflations, the presence and degree of mitral regurgitation after the procedure was less in group A (29 patients with no regurgitation or with grade I mitral regurgitation, and 5 with moderate and 1 with severe mitral regurgitation) than B (17 with no regurgitation or grade I mitral regurgitation, and 6 with moderate and 4 with severe mitral regurgitation). One patient from group A had a rupture of the anterior mitral leaflet leading to severe mitral regurgitation that needed emergency surgery. This finding was well depicted by TEE without new balloon inflations and contrast ventriculography (Figure 7). In 4 patients from group A and in 2 from group B, 2 jets of mitral regurgitation (1 central and another from a commissure) were detected.

After PMBV, mitral valve area was similar in both groups (2.2 ± 0.6 cm^2 in group A, and 2.0 ± 0.4 cm^2 in group B).

Maximal mitral leaflet separation increased after PMBV (before 0.50 ± 0.20 cm, and after 1.30 ± 0.40 cm; $p < 0.01$) (Figure 8).

After PMBV, the amount of spontaneous contrast within the left atrium had a tendency to decrease compared with before PMBV. This was very variable, depending on the size of the left atrium, cardiac rhythm and the final valve area. A significant increase in spontaneous contrast could be detected during each inflation of the balloon, which decreased immediately after balloon deflation. In 1 patient, a transient catheter-related thrombus was identified by TEE, resulting in additional heparin administration.

The mean procedure times were 45 and 50 minutes in groups A and B, respectively. The mean x-ray exposure times were 20 and 35 minutes in groups A and B, respectively ($p < 0.05$).

TEE was well-tolerated in all patients from group A, except 1 with very severe pulmonary hypertension; in this patient, TEE had to be interrupted because of transient respiratory depression and hypoxemia. The hemodynamic changes induced by TEE were as follows: The introduction of the endoscope was accompanied by: (1) increase in heart rate in 33 patients (94%; range 20 to 72 beats/min, mean 42); (2) increase in systolic left ventricular pressure in 25 patients (57%; range 22 to 74 mm Hg, mean 48); (3) increase in pulmonary artery pressure in 20 patients (57%; systolic: range 10 to 40 mm Hg, mean 28; and diastolic: range 5 to 12 mm Hg, mean 8); and (4) decrease in pulmonary artery oxygen saturation in 23 patients (65.7%; range 10 to 40%, mean 23%). These hemodynamic changes were transient (range 3 to 8 minutes, mean 5.2). The decrease in pulmonary artery oxygen saturation was significantly more marked in patients with pulmonary artery pressure >50 mm Hg (32 vs 15%; $p < 0.01$). The increase in pulmonary artery pressure was more marked in patients with a pressure >50 mm Hg (37 vs 14%; $p < 0.05$).

DISCUSSION

Although TEE has been used during PMBV to guide transseptal puncture, very few studies have analyzed the usefulness of TEE during PMBV. We studied 2 groups of patients who underwent PMBV, 1 aided by TEE (group A) and the other not (group B). This study showed that the intracardiac anatomy (especially the atrial septum and fossa ovalis) was more clearly and precisely displayed when PMBV was performed using cross-sectional echocardiographic imaging control. TEE was most useful in cases in which the anatomic relations of the cardiac chambers varied (large left atrium) and identification of the exact point for atrial septal puncture became difficult. All patients in group A had the atrial septal puncture in the fossa ovalis with a small residual atrial septal defect. Septal puncture in the muscular portion of the atrial septum was detected in some patients from group B. This type of puncture had a larger atrial shunt that may have an increased tendency to persist over time. Our experience suggests that the triangular configuration of the atrial septum (tent sign) indicates a good position for transseptal puncture.

Similarly, TEE helped in guiding the catheter balloon through the orifice of the mitral valve. Proper positioning of the balloon before inflation could be correctly assessed by TEE, preventing damage to the ventricular wall and subvalvular apparatus. Immediately after balloon inflation, maximal mitral leaflet separation could be measured as an index of successful mitral dilation, and the presence and degree of mitral regurgitation could be calculated without repeat left ventriculography. Patients in group A had less mitral regurgitation than did those in group B, despite a large number of balloon inflations and a similar final mitral valve area. Complications, such as tear of the mitral leaflets leading to severe acute mitral regurgitation, can occur. A rapid and reliable diagnosis can be obtained by TEE, enabling immediate surgical intervention if necessary. TEE identified other possible complications of PMBV, such as a transient, catheter-related thrombus in 1 patient. TEE significantly reduced x-ray exposure time by providing excellent visualization of intracardiac structures where the most critical steps of PMBV occur.

Overall, TEE was well-tolerated. Although cardiopulmonary complications associated with this technique occur seldom, the supine position used for PMBV could increase the risk of aspiration. We demonstrated that during transesophageal probe insertion, important transient hemodynamic changes occur. One patient in this study developed transient respiratory depression induced by TEE, which necessitated interruption of the examination.

Finally, the series with and without TEE were too small to conclusively demonstrate benefit in many areas. However, it appears clear that there is the potential to reduce complications and fluoroscopy time.

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Quantitative Dynamics of Left Ventricular Emptying and Filling as a Function of Heart Size and Stroke Volume in Pure Aortic Regurgitation and in Normal Subjects

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Quantitative understanding of the dynamics of left ventricular (LV) emptying and filling as the left ventricle dilates but maintains ejection fraction is limited. Cine computed tomography was used to quantify peak LV emptying and filling characteristics in 30 patients with normal ejection fraction but variable end-diastolic and stroke volumes. Group I consisted of 15 normal male patients and group II of 15 male patients with chronic, well-compensated, isolated aortic regurgitation. For each patient global LV volumes, absolute peak emptying and peak early diastolic filling rates and the timing of these maximal slopes were quantified. Mean arterial pressure and heart rate were within the normal range and ejection fraction and ages similar between groups I and II. Between-group analyses showed significantly increased end-diastolic and stroke volumes in group II compared with group I but nearly identical end-systolic volumes. Likewise, absolute peak emptying and filling rates were significantly greater in group II than in group I patients. The ratio of peak emptying rate to peak filling rate remained constant between groups. Timing of peak emptying and filling were similar in both groups. Absolute LV peak emptying and filling rates were found to vary linearly with end-diastolic and stroke volumes in all subjects examined. However, referencing peak emptying or peak filling rates to end-diastolic or total stroke volumes eliminated intergroup differences. Thus, in the presence of preserved ejection fraction and normal arterial pressure, the dynamic rates of LV emptying and early diastolic filling increase in direct proportion to absolute end-diastolic and stroke volumes, but the ratio of peak emptying to peak filling rate remains constant.

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The insidious development of left ventricular (LV) dilatation in response to an applied hemodynamic load is, to a point, considered a proper adaptive mechanism. Such changes in adults are frequently noted in the presence of isolated aortic valvular regurgitation, but knowledge of what is the "proper" adaptation for dynamic rates of systolic emptying and early diastolic filling as the left ventricle dilates and maintains ejection fraction is limited. Compensatory mechanisms undoubtedly enter when defining dynamics of LV emptying and filling during normal growth and development to parallel necessary changes in LV size and muscle mass. It is not known to what extent this type of physiologic compensation occurs in the asymptomatic volume overload seen in many adults with isolated valvular regurgitation. The present study examines the dynamics of LV emptying and filling in patients with normal ejection fraction as a function of LV size and stroke volume.

METHODS

Patients: Fifteen normal adult, male subjects (group I) were recruited for participation as control subjects in protocols regarding the assessment of left and right ventricular function using cine computed tomography (CT) as approved by the institutional review board. To be considered "normal," each subject had to have a normal resting heart rate, electrocardiogram, systemic arterial pressure, cardiac and pulmonary physical examination, no personal history of cardiovascular disease and no family history of early onset coronary artery disease.

Additionally, twenty-three adult patients with chronic and isolated aortic value regurgitation were recruited for a study comparing quantitation of cine CT regurgitant volumes with parameters derived using Doppler echocardiography.[1] For entry into the protocol, the patients could have no other significant systemic or valvular diseases. All patients had a thorough history and physical examination, a resting electrocardiogram, a careful 2-dimensional/Doppler echocardiographic study, and an ultrafast CT examination. Of the original patient group, a subset of 15 male patients (group II) with isolated aortic regurgitation were identified who were asymptomatic, had an LV ejection fraction within the normal range, had no obvious regional wall motion abnormalities by 2-dimensional echocardiography or ultrafast CT, and had ages similar to the group of normal subjects.

Cardiac imaging: Cine (also called "ultrafast") CT, which provides high spatial and temporal resolution im-

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ages of the heart, was used to quantify LV emptying and filling dynamics. Electrocardiographic triggering at the R wave (end-diastole) allows for serial acquisition of polytomographic images of the heart at a rate of 17 frames/s. Each tomographic level is 0.8 cm thick with a center-to-center distance between levels of 1.0 cm; the orientation of each contiguous tomogram is automatically referenced in a 3-dimensional space during scanning. Analyses of these images have been shown to provide quantitative data on LV[2] and right ventricular[3] muscle mass, left and right ventricular tomographic and global stroke volumes,[4-6] cardiac output,[7] regional[5,8] and global[4-7,9] LV function and wall thickening and absolute and relative rates of early diastolic filling at rest in humans.[10-12]

Imaging of each subject was done in a fashion as previously described.[5,7-13] No premedications were given and subjects were instructed to fast before the study. Self-adhering electrode pads were placed on the chest to allow for continuous electrocardiographic monitoring and to act as a triggering signal to the scanner. After placement of an 18 gauge, 5 cm catheter in a right antecubital vein, each subject was positioned in the scanner so as to facilitate acquisition of LV short-axis (transverse cardiac) images from apex to base.[14] A non-contrast localization scan was performed to determine the level of the LV apex. The subject was then mechanically moved into the scanner to assure that the most caudad tomographic image was obtained at the level of the cardiac apex. This assures that all subjects are imaged in a uniform fashion.

After positioning and determination of a "circulation time"[3,5,7,10-13] a powered injector delivered an infusion of nonionic contrast medium (Iohexol-350, Sterling Winthrop or Iopamidol-370, E.R. Squibb & Sons) at 0.5 ml/kg for 20 seconds. Commencing image acquisition at the circulation time assured excellent opacification of both the left and right ventricular cavities at all levels scanned. Imaging, initiated at the electrocardiogram R wave, consisted of 13 consecutive frames through the cardiac cycle at 6 separate tomographic levels. After a 2- to 5-minute interval, the scanning table was moved 6 cm and the scanning sequence repeated. The normal human left ventricle is roughly 10 to 12 cm from the tip of the epicardial apex through the origin of the aortic root, just cephalad to the aortic valve. For normal subjects therefore, only 2 scan series were necessary to image the entire heart; however, for many of the patients with isolated aortic valvular regurgitation and LV dilatation, 3 consecutive and contiguous scan series (spanning 18 cm from apex to base) were necessary to examine the entire heart.

Data analysis: At each tomographic level the LV endocardial surface was identified and planimetered from each scan acquired during the cardiac cycle using a previously validated algorithm.[2-6] These endocardial surface areas were converted to tomographic volumes after multiplying by the center-to-center distance between images; the data were then entered into a computer-based relational database. In the database, the individual tomographic volumes defined from all levels from LV apex through base at each time from end-diastole (0% of the cardiac cycle) were listed in rows. A global LV volume versus time (from end-diastole) column was defined by the sums of each volume at each cardiac time point examined (the timing of each scan with respect to the cardiac cycle was provided from the file header information recorded with each scan).

Concomitant with definition of LV volumes at each tomographic level, right ventricular volumes were determined in the group II patients according to the method of Reiter et al.[4] Definition of absolute LV regurgitant volumes was then determined by subtracting the stroke volumes of the left and right ventricles, as previously described.[6]

The global LV volume versus time data were reviewed for completeness from end-diastole to end-systole and throughout at least the early rapid filling phase of diastole (i.e., is the CT volume data sufficiently complete so that the last time point begins to plateau into diastasis during the midportion of diastole?). This test was performed in all patients in each group. At normal resting heart rates, the data from 13 consecutive 58 ms intervals does not necessarily constitute data from an entire cardiac cycle. In those situations, the data were "padded" from the last time point (image 13) to the end-diastolic volume, assuming a linear phase of diastasis for a known individual heart rate. The data were then regressed using an 8 harmonic Fourier series (or Fourier interpolator) and 128 equally spaced points generated along the regressed LV volume versus time curve. Definition of the timing and slope of the fastest rate of systolic emptying (maximal negative slope) and early diastolic filling (maximal positive slope during rapid filling phase) were determined by calculating the slope on a point-by-point basis for each of the 128 time points. Volumes (and subsequent timing) at end-diastole (largest volume during the cardiac cycle) and end-systole (nadir of the volume during the cardiac cycle) were determined directly from the interpolated volume/time curve (Figure 1). The choice of an 8 harmonic curve fit was chosen to satisfy the Nyquist sampling theorem considering the cine CT sampling rate of 17 frames/s. This theorem limits the highest frequency that can be determined to one-half the sampling rate. For a heart rate of 1 beat/s (i.e., 60 beats/min) the upper limit of frequency response is thus limited to approximately 8 Hz.

The applicability of cine CT to quantitate early diastolic filling at normal resting heart rates in humans has been previously published.[10,11] Use of Fourier techniques as applied to analysis of the volume-time data using cine CT has been shown to be quantitatively identical to results derived using a standardized radionuclide angiography method.[12] Although no specific comparison was performed for quantitation of peak LV emptying rates, it was assumed that similar results would be found when comparing cine CT and radionuclide angiography for systolic emptying.

Statistical analysis: Data are presented as mean ± standard deviation. The time during the cardiac cycle of peak emptying or filling, or both, was normalized to the square root of the RR cycle length (by analogy to normalization of the QT interval of the electrocardiogram).

A Student's *t* test was used for comparisons between the subject groups I and II. Linear correlations were performed using a least-squares fit and Pearson's correlation coefficient. A p value <0.05 was defined as the level of statistical significance.

RESULTS

Baseline statistics and hemodynamics: The average age for patients in group I was 25 ± 4 years (range 23 to 35), whereas the average age for patients in group II was 29 ± 6 years (range 19 to 40). Global ejection fractions for each patient group were normal and similar (73 ± 6 and 68 ± 6% for groups I and II, respectively). Mean arterial pressures were in the normal range for both group I and II subjects (110 ± 7 and 119 ± 11 mm Hg, respectively [p = 0.02]); average heart rates were 67 and 60 beats/min, respectively (p = 0.03). Values for either of these variables immediately after any scanning period changed in a given subject by <10%. Thus, volumetric data derived from the sum of 2 or 3 scans per patient were assumed to be acquired under stable loading conditions for each patient. Because of minor but significant differences in heart rates between the 2 subject populations, data regarding timing of peak emptying and filling during the cardiac cycle in all subjects were normalized by the square root of the RR interval. In group II patients with LV enlargement secondary to isolated aortic regurgitation, 4 had mild (<20 ml/stroke, range 4 to 16), 3 had moderate (20 to 40 ml/stroke, range 22 to 37) and 8 had severe (>40 ml/stroke, range 43 to 139).

Global systolic and diastolic dynamics between patient groups: Mean global end-diastolic, end-systolic and stroke volumes for groups I and II are listed in Table I. The average rates and timing for peak LV emptying and filling are listed in Table II. As would be expected, end-diastolic and stroke volumes were significantly different between each subject group but end-systolic volumes were similar. Additionally, absolute peak emptying and peak (early diastolic) filling rates were significantly greater in group II. The ratio of peak emptying rate to peak filling rate, however, was nearly identical between groups, suggesting parallel changes

TABLE I Comparison of Absolute End-Diastolic, End-Systolic and Stroke Volumes Between the Two Patient Groups Examined

	EDV (ml)	ESV (ml)	SV (ml)
Normal LV (group I)	135 ± 34	64 ± 33	71 ± 11
Enlarged LV (group II)	234 ± 55	75 ± 26	158 ± 35
p value (group I vs II)	<0.001	0.302 = NS	<0.001

EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricle; NS = not significant; SV = stroke volume.

TABLE II Peak Left Ventricular Emptying and Early Diastolic Filling Rates and Timing of Maximal Emptying and Filling Rates from End-Diastole Within the Two Patient Groups Examined

	PER (ml/sec)	PER (ml/sec)	PER/PFR	TPE (sec)	TPF (sec)
Normal LV (group I)	400 ± 73	330 ± 71	1.26 ± 0.33	0.15 ± 0.04	0.48 ± 0.09
Enlarged LV (group II)	842 ± 191	692 ± 179	1.26 ± 0.30	0.16 ± 0.04	0.49 ± 0.04
p value (groups I vs II)	<0.001	<0.001	0.96 = NS	0.31 = NS	0.73 ± NS

PER = peak emptying rate; PFR = peak early diastolic filling rate; TPE = timing of maximial emptying; TPF = timing of maximal filling; other abbreviations as in Table I.

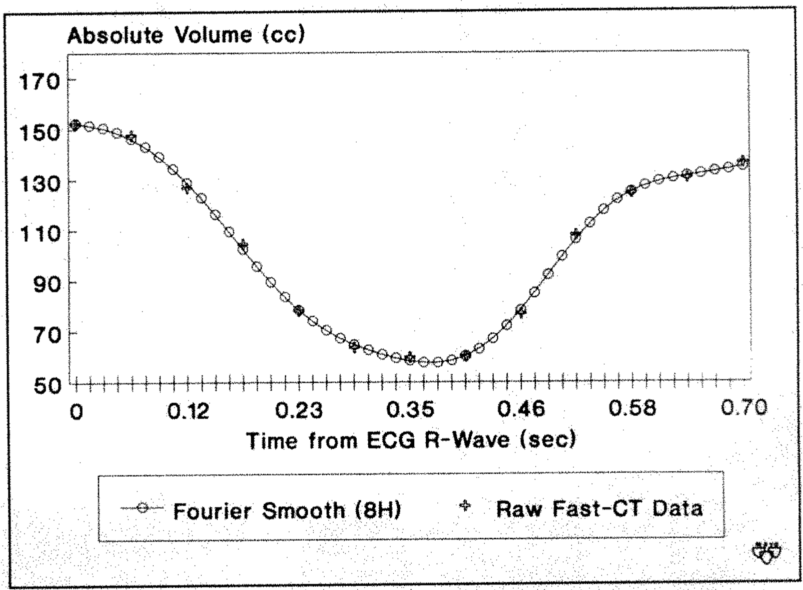

FIGURE 1. Time-dependent global left ventricular volume curve in a normal patient showing the "raw" (nonsmoothed) data from the cine computed tomography (CT) examination and the results of the 8 harmonic Fourier smoothing interpolation. Note the excellent reproducibility of the computed tomography data from the interpolation. ECG = electrocardiographic.

between emptying and filling dynamics as the left ventricle enlarges. Timing (from the R wave of the electrocardiogram) of peak emptying and filling was not different between the 2 groups. This suggests that systolic emptying and diastolic filling, at least in patients with normal ejection fraction, normal arterial pressure and no regional wall motion abnormalities, follows a similar time course during the cardiac cycle regardless of LV size.

To examine the potential for differences between patient groups regarding a dependency of absolute peak emptying and peak filling rates on LV size and stroke volume, data from the 2 patient groups were normalized to absolute end-diastolic and stroke volumes (Figure 2). Once referenced for these 2 individual characteristics of the left ventricle, the ratio of peak emptying and peak filling rates to end-diastolic volume (or to stroke volume) were not significantly different between groups I and II.

Peak emptying and filling dynamics as a function of end-diastolic and stroke volumes: Figure 3 shows a direct relation between peak emptying rate and peak filling rate versus stroke volume in all subjects examined. Figure 4 shows a similar relation for peak emptying and peak filling rates versus end-diastolic volume. These parameters which characterize the patterns of LV emptying and (early) diastolic filling are shown to be direct linear functions of LV size and systolic stroke volume, at least in the presence of normal ejection fraction.

LV ejection fraction is often used as a measure of overall LV function, but a direct relation to peak emptying or peak filling rates has only been suggested.[15,16] Ejection fraction is stroke volume normalized to LV size (i.e., end-diastolic volume); thus, it is reasonable to compare ejection fraction to values of peak emptying and peak filling rates that also have been referenced to LV size. Figure 5 shows the ratio of peak emptying and peak filling rates to end-diastolic volume versus individual global ejection fraction. As may have been predicted, the ratio of peak LV emptying rate to end-diastolic volume and ejection fraction do, in fact, have a direct and positive correlation, however, the scatter within the results suggests that this may not be useful for clinical comparisons. Although these results have demonstrated a nearly constant relation between absolute peak emptying and peak filling rates (roughly 1.26:1, see Table II), when attempting to correlate the ratio of peak filling rate and end-diastolic volume to ejection fraction, no clear relation was determined. This may be because the ratio of peak filling rate to end-diastolic volume was relatively constant over the range of normal ejection fractions required in the groups examined.

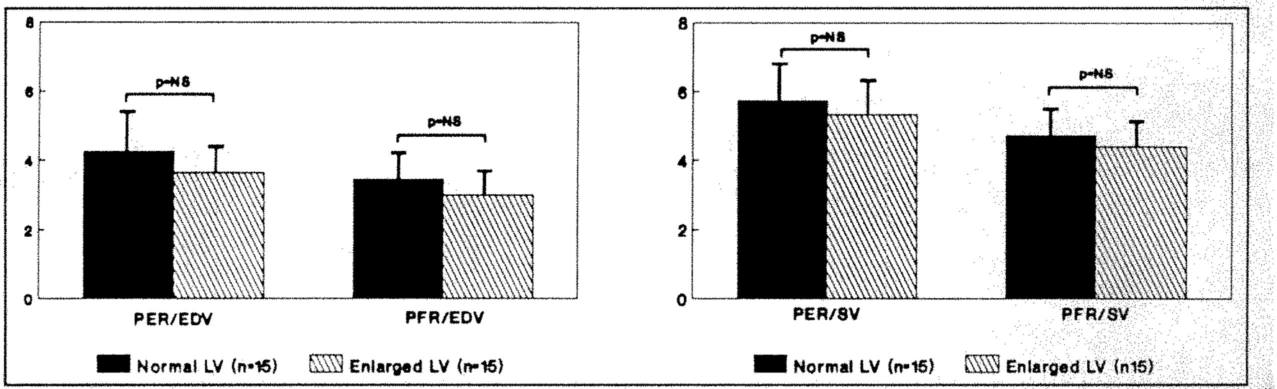

FIGURE 2. Referencing of peak left ventricular emptying rate (PER) and peak early diastolic filling rate (PFR) to absolute end-diastolic volume (EDV) *(left panel)* and stroke volume (SV) *(right panel)* for the 2 patient groups. Note that after referencing, the peak emptying and peak filling rates are independent of left ventricular size and stroke volume. LV = left ventricle; NS = not significant.

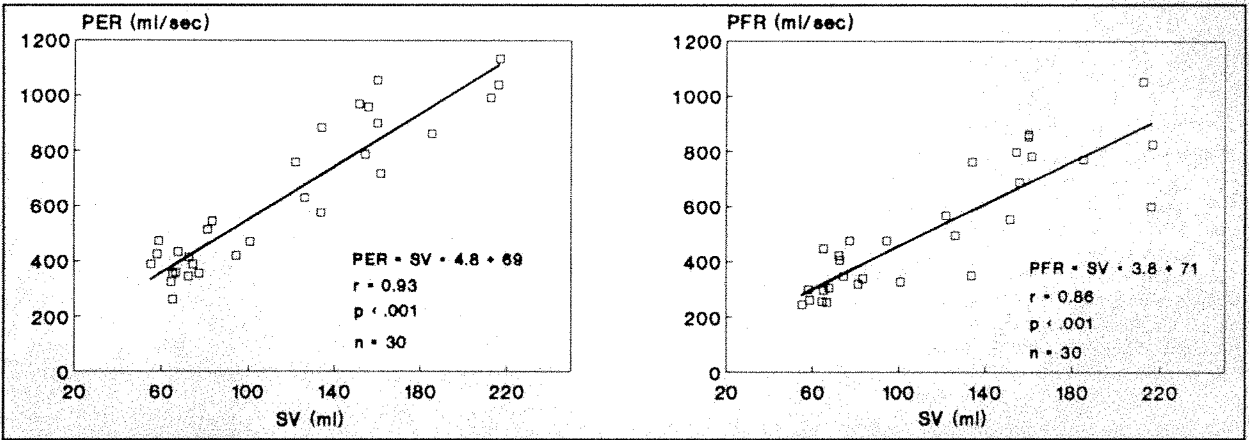

FIGURE 3. Linear correlations between absolute left ventricular peak emptying rate (PER) and peak early diastolic filling rate (PFR) with stroke volume (SV) in all subjects examined. Note that as stroke volume increases, both peak emptying and peak filling rates increase proportionately.

DISCUSSION

There are 2 major observations from the current study. First, the maximal rates of LV systolic emptying and early diastolic filling, in the presence of normal arterial pressure and normal ejection fraction, are directly proportional to both stroke and end-diastolic volumes over a very broad physiologic range. This proportionality is maintained despite the fact that absolute peak LV filling rate is approximately 25% < peak emptying rate. In response to an elevated end-diastolic volume or necessary increase in stroke volume to maintain forward cardiac output, the left ventricle could change both the speed of contraction or relaxation, or both, and the relative time during the cardiac cycle at which these occur. Second, from the current data, the time from end-diastole to maximal LV emptying rate and maximal early diastolic filling rate remains fixed over a broad physiologic range for stroke and end-diastolic volumes.

The results from the current study indicate a direct relation between peak rates of LV emptying and early diastolic filling on end-diastolic or stroke volumes, or both. But, total stroke volume rather than absolute LV size was seen as a better predictor of peak rates of ejection and filling during the cardiac cycle. This is not particularly surprising since the duration or timing of ejection and filling was relatively constant between the 2 groups despite significant differences in end-diastolic and stroke volumes. Although in the presence of isolated aortic regurgitation, the isovolumetric relaxation period may be lengthened, the timing of the peak filling rate from end-diastole (time to peak filling, see Table II) was found to be relatively constant. It therefore should be expected, in order to accommodate expulsion of an increased stroke volume within a narrow time window during the cardiac cycle, that the maximal dynamic rates of volume change should increase proportionally.

The dependency of peak emptying and filling rates on end-diastolic volume could be predicted from the baseline data. As noted, end-systolic volumes were not statistically different between the 2 subject groups (Table I). Because stroke volume is end-diastolic volume minus end-systolic volume, a direct relation between stroke and end-diastolic volumes would be expected if end-systolic volume remained constant.

The ratio of peak emptying to peak filling rates remained the same regardless of LV size and stroke volume. At relatively normal heart rates, as in this study,

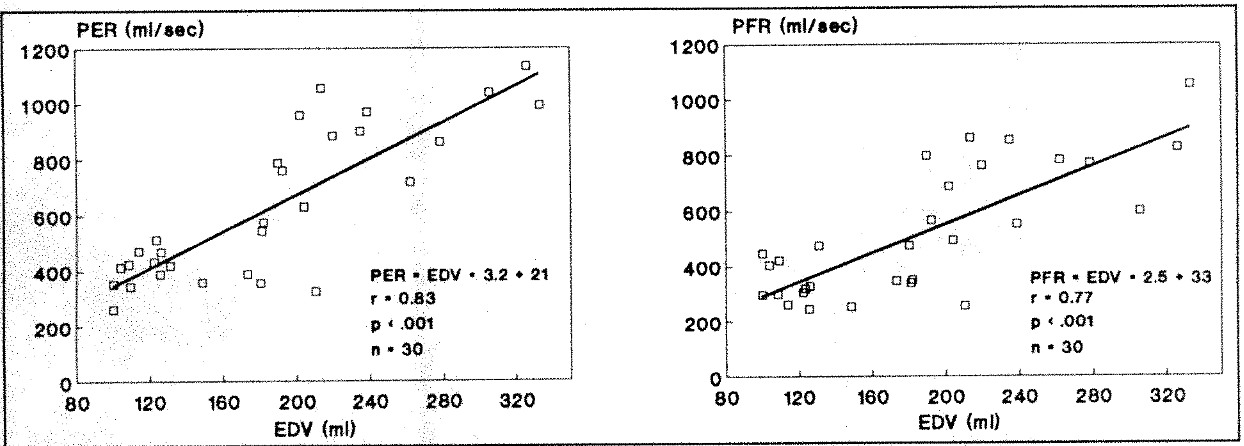

FIGURE 4. Linear correlations between absolute left ventricular peak emptying rate (PER) and peak early diastolic filling rate (PFR) with end-diastolic volume (EDV) in all subjects examined. Note that as overall left ventricular size increases, both peak emptying and peak filling rates increase proportionately.

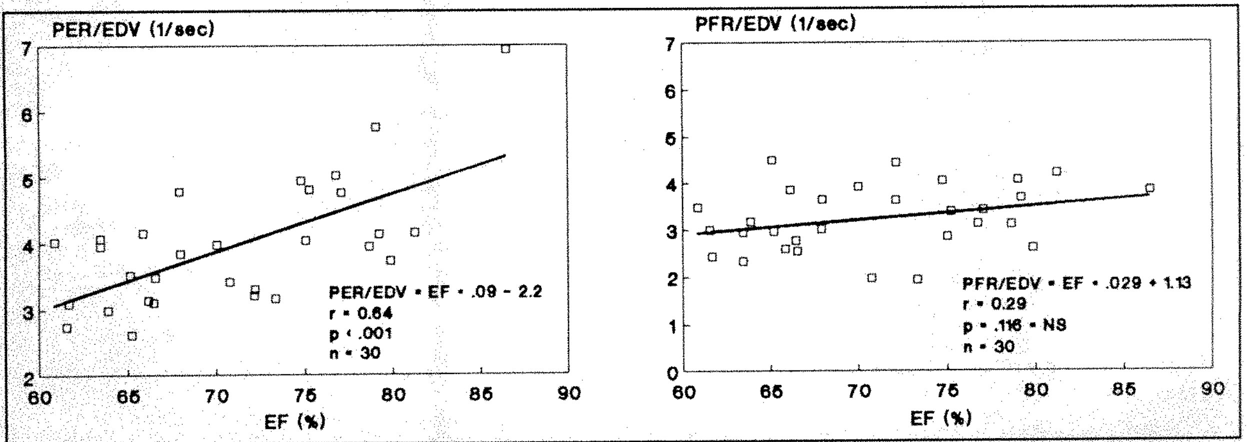

FIGURE 5. Linear correlations between absolute left ventricular peak emptying rate (PER) and peak early diastolic filling rate (PFR) referenced to global end-diastolic volume (EDV) as a function of global ejection fraction (EF) in all subjects examined. Note that there is a positive but weak correlation between peak emptying rate/end-diastolic volume and ejection fraction; however, this correlation is not seen for peak filling rate/end-diastolic volume. NS = not significant.

approximately 80% of the total diastolic filling (which equals stroke volume) has been completed by the end of the rapid filling phase. One might then predict maximal peak filling rate to exceed early diastolic filling rate by 1.25-fold (i.e., 1/0.8). In the current study the ratio of peak emptying rate/peak filling rate was approximately 1.26 in both patient groups (see Table II). This would suggest that adjustments in peak emptying and peak filling rates occur in a uniform and parallel fashion in normal subjects and in patients with well-compensated aortic regurgitation and volume overload hypertrophy.

Potential sources of error in the current study fall into 3 areas. The first is the accuracy of LV volumes used as input into the analysis. However, the Simpson's rule approximation has been shown to be quantitatively accurate using echocardiography,[17] magnetic resonance imaging[18] and especially with Cine CT in defining cardiac mass, volumes and ejection fraction.[2-6,9] The actual values for peak emptying and peak filling rates given from the current investigation are in quantitative agreement with those previously published using cineangiography[15,16] and 2-dimensional echocardiography.[19,20] Bacharach[21] and Bonow[22] and their colleagues suggested that definition of absolute LV filling (and emptying) rates may be underestimated using cine CT sampling rates (17 frames/s), especially with exercise. But, we believe that at heart rates of between 60 and 70 beats/min, as were examined in the current investigation, the magnitude of errors using cine CT was probably small; additionally, each data set from each patient was carefully analyzed in a consistent fashion by the same person. Finally, the ability to define the dynamic response of the left ventricle to chronic changes in LV size and stroke volume in the current study relies on the appropriateness of comparing normal patients to patients with isolated aortic regurgitation. There is no way, in advance, to assure that patients with regurgitation had no abnormalities in LV compliance that might confound results of this study. An attempt was made to define patients whose primary differences between groups were confined to LV size and stroke volume (i.e., patients in groups I and II had very similar, although not identical, ages, ejection fractions, heart rates and mean aortic pressures). Within the confines of these limitations, the results of the current investigation are considered to be accurate.

The clinical importance of these measurements is in the justification of the frequently used referencing of peak LV emptying and filling rates to ventricular volumes to facilitate comparisons between patients and across time in a given patient. However, use of stroke volume rather than end-diastolic volume appears to be a more reliable reference for changes in dynamics of LV emptying and filling. A serial reduction in these parameters may be any early indicator of decompensation in patients with previously stable and well-tolerated aortic regurgitation.

Acknowledgment: We wish to acknowledge the efforts of the technologists in both the echocardiography and ultrafast CT laboratories. This study is dedicated to the memory of Melvin L. Marcus, MD, who, as the great mentor he was, inspired us to use technology to "learn something about how the heart works."

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Effects on Platelet Aggregation and Fibrinolytic Activity During Upright Posture and Exercise in Healthy Men

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The circadian variation of acute myocardial infarction suggests that daily activities such as assuming the upright posture and performing different daily activities may trigger the onset of coronary thrombosis. Such triggering may result from unfavorable alterations in the balance between the prothrombotic and antithrombotic properties of the blood. The present study compares the effects of 2 common daily activities, assuming the upright posture and exercise, on platelet aggregation and fibrinolytic activity. In healthy male subjects, assuming the upright posture in the morning significantly increased platelet aggregation and produced only a moderate increase in fibrinolytic activity within 10 minutes. These changes were still present after 90 minutes in the upright posture. Supine posture for 45 minutes resulted in levels of fibrinolytic activity and platelet aggregation comparable to that observed before initially assuming the upright posture in the morning. Return to the supine posture for 45 minutes resulted in levels of fibrinolytic activity and platelet aggregation comparable to that observed before the initial assumption of upright posture. The changes recurred when upright posture was taken later in the day.

Exercise did not increase platelet aggregation to levels beyond that produced by the upright posture, but was associated with a marked increase in fibrinolytic activity. Thus, exercise and upright posture produce distinctive alterations in the thrombogenic potential of the blood that may influence the timing of clinical vascular events.

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The frequencies of onset of myocardial infarction and sudden cardiac death have a prominent circadian variation, with an increase in the period from 6 A.M. to noon.[1,2] During this time period, subjects assume the upright posture and perform physical exertion — 2 activities that activate the sympathetic nervous system and may cause systemic changes in blood clotting that predispose to coronary artery thrombosis.[3,4] Assumption of the upright posture in the morning is associated with increased platelet aggregability.[4] However, the ability of the upright posture to increase fibrinolytic activity, a change that would tend to reduce the thrombotic potential of the blood, has not been previously described. Although it is agreed that exercise increases fibrinolysis,[5,6] the effects of exercise on platelet aggregation are controversial.[7-11]

The goals of this study, therefore, were to answer the following questions concerning the effects of the upright posture and exercise on platelet aggregability and fibrinolysis: (1) What is the time course of the effect of the upright posture in the morning on platelet aggregability? (2) Does assuming the upright posture at a later time of day cause a similar increase? (3) Is the adverse effect, if it occurs, of assuming the upright posture on platelet aggregability counterbalanced by an increase in fibrinolytic activity? (4) Does exercise produce an increase in platelet aggregability beyond that produced by the upright posture? (5) What are the relative profiles of the effects of the upright posture and exercise on these determinants of thrombosis?

METHODS

This report describes 2 studies of 12 male volunteers, each drawn from a total pool of 22 subjects, aged 20 to 32 years (mean 24), who were all nonsmokers, and taking no aspirin or other medication in the previous 2 weeks. All had given informed consent. On the day before the study, all subjects were admitted to the Clinical Research Center of the Brigham and Women's Hospital. Lights were turned out at midnight, and subjects were awakened at 7:30 A.M. the following morning for initiation of the study. After arrival at the hospital, the subjects received a controlled fixed diet. The subjects did not drink any coffee, tea or hot chocolate after they were awakened on the study morning. Coffee was not provided during the study; however, tea and chocolate were available in the evening before the study. The effects of these agents would have have worn off before the morning studies, during which 250 ml of juice and drinking water were available.

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Phase I was designed to determine (1) the time course of the effect of the upright posture in the morning on plasma catecholamine levels and platelet aggregability; and (2) whether the upright posture at a later time of day causes similar changes. After waking at 7:30 A.M., the 12 subjects remained supine for 30 minutes. Then, they assumed the upright posture, remained upright until 9:30 A.M., lay supine until 11:30 A.M., and returned to the upright posture for 90 minutes at the end of the protocol (Figure 1). Blood samples were obtained at 8 A.M. while the subjects were still supine in bed, and after 6, 45 and 90 minutes in the upright position. Blood samples were then obtained after 2 hours in the supine position, and finally 90 minutes after patients had returned to reassume the upright posture.

Phase II was designed to determine (1) whether the adverse effect of the upright posture on platelet aggregability is associated with an increase in fibrinolytic activity; (2) if exercise produces an increase in platelet aggregability beyond that produced by the upright posture; and (3) the relative profiles of the effects of the 2 activities — upright posture or exercise — on platelet aggregability and fibrinolytic activity.

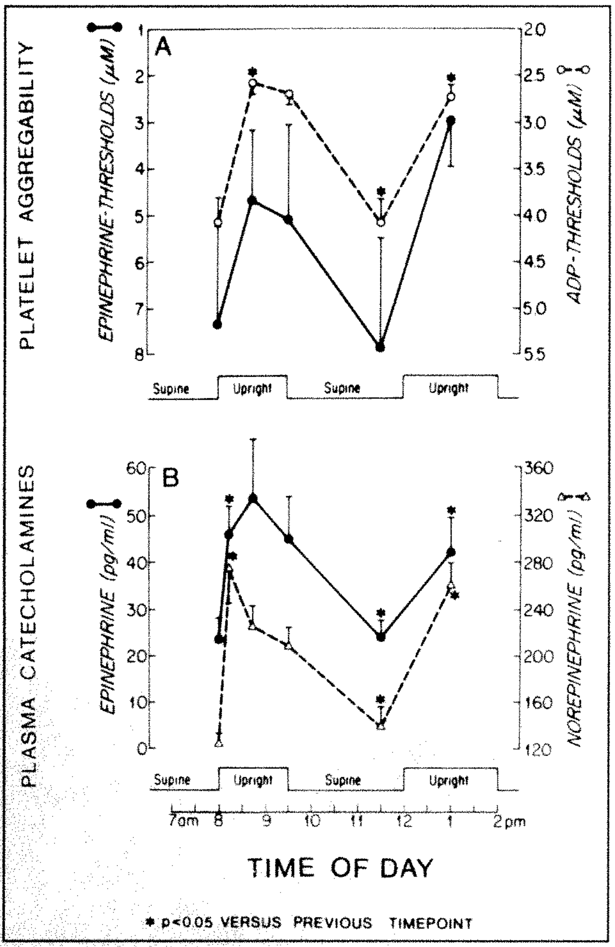

FIGURE 1. Platelet aggregation, indicated as adenosine diphosphate (ADP) and epinephrine threshold values and plasma epinephrine and norepinephrine, observed during phase I. Assumption of the upright posture in the morning, or later, produces a marked increase in all 4 variables at different time points (values are mean ± SEM, n = 12).

After they were awakened at 7:30 A.M., 12 subjects (2 of whom participated in phase I) remained in bed for 30 minutes. Then, they assumed the upright posture (as in phase I), remained upright for 90 minutes, lay supine for another 45 minutes, returned to the upright posture for 90 minutes, and then performed a standardized bicycle test (Figure 2). Blood samples were obtained at 8 A.M. while the subjects were still supine in bed, at 10 and 90 minutes after taking the upright posture, and 10 and 45 minutes after they returned to the supine position. At 11:45 A.M., after being in the upright posture for 90 minutes, they were placed on a cycle ergometer with a mechanically controlled brake to regulate the work load. Blood was drawn at 11:55 A.M., immediately before exercise, and again at 12:05 P.M. immediately after exercise. The initial work load of 50 W was increased by 50 W every 3 minutes of exercise. Subjects exercised until approximately 90% of maximal working capacity was achieved (mean exercise duration 10.4 minutes). Blood pressure was measured at 8:02 A.M. (2 minutes after assuming the upright posture), at 11:55 A.M. while sitting on the bicycle, and immediately after exercise using a mercury sphygmomanometer; heart rate was determined at the same time points.

Blood sampling: Blood samples were drawn without stasis from an antecubital vein with the use of a 21 gauge butterfly needle, and processed immediately. Separate venipunctures were performed at each time point. Twenty-seven milliliters of blood was drawn into a plastic syringe containing 3 ml 3.8% sodium citrate for platelet aggregation and euglobulin clot lysis time. Samples of 5 ml were collected in alternate syringes for analysis of catecholamines, plasma renin activity, hematocrit value and platelet count; and another 5 ml sample was drawn for tissue-type plasminogen activator antigen and plasminogen activator inhibitor activity. Platelet aggregation, plasma catecholamines, renin activity, hematocrit and platelet count were determined as previously described.[3,4] Euglobulin clot lysis time was estimated according to normal laboratory routine.[12] Tissue-type plasminogen activator antigen (ELISA) and plasminogen activator inhibitor activity (chromogenic method) were determined using reagents from the STAGO Diagnostic System.

Statistical analysis: Comparison between the mean values at different time points was performed with the Wilcoxon signed rank test for paired data. Variations from mean values are expressed as ± standard error of the mean. Two-tailed p values ≤ 0.05 were regarded as statistically significant.

RESULTS

Phase I: time course of platelet aggregability and catecholamine changes: PLATELET AGGREGABILITY: Adenosine diphosphate–induced platelet aggregability significantly increased after 45 minutes in the upright position as indicated by a decrease in mean adenosine diphosphate threshold concentrations from 4.1 ± 0.4 to 2.7 ± 0.2 μM ($p < 0.01$) (Figure 1). A similar pattern was observed for epinephrine-induced platelet aggregation. Mean epinephrine threshold decreased from 7.4 ±

TABLE I Platelet Aggregation, t-PA Antigen, Inhibitor Against t-PA (plasminogen activator inhibitor), Platelet Count, Hematocrit, and Plasma Epinephrine, Norepinephrine and Renin are Given at Different Time Points for Subjects During Phase II

	Supine (8 A.M.)	Upright (8.10 A.M.)	Upright (9.30 A.M.)	Supine (9.40 A.M.)	Supine (10.15 A.M.)	Upright (11.55 A.M.)	Exercise (12.05 P.M.)
Platelet aggregation (ADP thresholds μM)	5.4 ± 0.6	4.0 ± 0.5	4.4 ± 0.4	4.0 ± 0.4	5.2 ± 0.2†	4.3 ± 0.4*	3.8 ± 0.4
t-PA antigen (ng/ml)	4.7 ± 1.2	7.7 ± 1.7*	5.9 ± 1.7	4.9 ± 1.2*	4.7 ± 1.3	4.9 ± 1.1	17.7 ± 4.0†
PAI activity (IU/ml)	1.06 ± 0.4	0.97 ± 0.3	0.94 ± 0.3	1.09 ± 0.4	0.80 ± 0.4	0.63 ± 0.3	0.77 ± 0.2
Platelet count ($10^3/mm^3$)	261 ± 16	295 ± 90*	285 ± 16	273 ± 17*	275 ± 18	293 ± 21*	345 ± 20†
Hematocrit (%)	42.8 ± 0.61	44.0 ± 0.61*	44.3 ± 0.71	43.3 ± 0.61*	42.9 ± 0.51	43.8 ± 0.6*	47.1 ± 0.7*
Plasma epinephrine (pg/ml)	32.2 ± 4.8	54.0 ± 5.6*	50.5 ± 8.3	33.0 ± 7.1*	28.5 ± 1.9	42.5 ± 5.1*	213 ± 34†
Plasma norepinephrine (pg/ml)	164 ± 23	310 ± 40*	335 ± 47	207 ± 31*	202 ± 26	295 ± 32*	1670 ± 314†
Plasma renin activity (nl/ml/hour)	1.14 ± 0.2	1.45 ± 0.2*	2.88 ± 0.6*	2.28 ± 0.4	1.40 ± 0.4*	2.73 ± 0.7*	3.38 ± 0.5

*$p < 0.05$ versus previous time point; †$p < 0.05$ versus 9:30 A.M.
Values are mean ± SEM, n = 12.
ADP = adenosine diphosphate; PAI = plasminogen activator inhibitor; t-PA = tissue-type plasminogen activator.

2.2 to 4.7 ± 1.5 μM ($p < 0.06$). Return to the supine posture for 2 hours was sufficient to permit return of platelet aggregability to the level observed after the 8-hour overnight supine period (Figure 1). Finally, reassumption of the upright posture produced an increase in aggregability indistinguishable from that observed after initially assuming the upright posture.

PLASMA CATECHOLAMINE LEVELS: There was a marked surge in the levels of plasma catecholamines after assuming the upright posture. Within 10 minutes, plasma epinephrine and norepinephrine more than doubled (Figure 1, $p < 0.02$). Return to the supine posture for 2 hours resulted in a reduction in values to levels comparable to those observed at 8 A.M., whereas subsequent return to the upright posture resulted in a similar pattern to that observed earlier in the day (Figure 1, $p < 0.01$).

Phase II: platelet aggregability, fibrinolytic activity, and the effect of exercise: PLATELET AGGREGABILITY: Platelet aggregability increased 10 and 90 minutes after initial assumption of the upright posture as indicated by a decrease in the mean threshold values of adenosine diphosphate and epinephrine (Table I, Figure 2). Return to supine posture for 10 minutes did not alter platelet aggregation; however, aggregation returned to initial 8 A.M. levels after 45 minutes in the supine position (Table I, Figure 2). When subjects reassumed the upright posture, the changes in platelet aggregation were comparable to those observed after initial assumption of the upright posture. Exercise, however, did not cause a further increase in platelet aggregation as indicated by similar threshold concentrations of 4.3 ± 0.4 and 3.8 ± 0.4 μM for adenosine diphosphate and 1.0 ± 0.2 and 1.1 ± 0.4 μM for epinephrine (Table I, Figure 2).

FIBRINOLYTIC ACTIVITY: Fibrinolytic activity increased 10 minutes after initially assuming the upright posture as indicated by a shortening of the euglobulin clot lysis time from 130 ± 20 to 95 ± 17 minutes ($p < 0.02$) (Figure 2) and an increase in tissue-type plasminogen activator antigen from 4.7 ± 1.2 to 7.7 ± 1.7 ng/ml ($p < 0.01$) without a corresponding change in plasminogen activator inhibitor activity (Table I). These changes were less pronounced 90 minutes after assuming the upright posture. Return to the supine posture for 45 minutes resulted in tissue-type plasminogen activator levels similar to those observed before the initial assumption of upright posture in the morning (Table I). Returning to the upright posture resulted in euglobulin clot lysis time changes similar to those noted at the initial upright posture. Exercise caused a marked shortening of the euglobulin clot lysis time and an increase in tissue-type plasminogen activator antigen from 4.9 ± 1.1 to 17.7 ± 4.0 ng/ml ($p < 0.01$) (Figure 2, Table I). Plasminogen activator inhibitor activity did not change significantly after either assuming the upright posture or exercising (Table I).

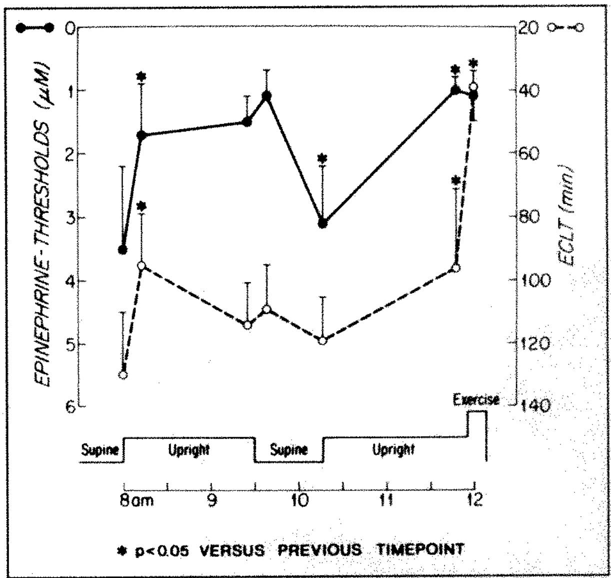

FIGURE 2. Simultaneous changes in platelet aggregability (epinephrine threshold values) and fibrinolysis (euglobulin clot lysis time [ECLT]), accompanying posture changes and exercise in phase II. Assumption of the upright posture increases both fibrinolysis and platelet aggregability, whereas exercise increases only the former (values are mean ± SEM, n = 12).

PLASMA CATECHOLAMINE AND RENIN CHANGES: Assuming the upright posture resulted in an increase in plasma catecholamines comparable to that observed in phase I, whereas exercise increased the plasma catecholamine level more than fivefold (Table I). An increase in plasma renin activity was observed after 10 and 90 minutes in the upright posture ($p < 0.01$). This increase reverted to the resting level after 45 minutes in the supine position ($p < 0.05$) (Table I). Returning to the upright posture produced a similar increase to that observed earlier in the day, whereas exercise did not significantly influence plasma renin activity (Table I). Assuming the upright posture did not affect systolic blood pressure but resulted in an increase in heart rate from 57 ± 2 to 71 ± 2 beats/min ($p < 0.01$) and in diastolic blood pressure from 73 ± 2 to 77 ± 1 mm Hg ($p < 0.01$). During exercise, increases occurred in heart rate from 82 ± 3 to 140 ± 3 beats/min ($p < 0.01$), systolic blood pressure from 113 ± 4 to 168 ± 8 mm Hg ($p < 0.01$), and diastolic blood pressure from 70 ± 3 to 81 ± 4 mm Hg ($p < 0.01$).

HEMATOCRIT AND PLATELET COUNT: As expected, the upright posture resulted in an increase in platelet count and hematocrit value of 12.6% ($p < 0.01$) and 2.6% ($p < 0.01$), respectively; whereas exercise resulted in an increase in the same parameters of 17.7% ($p < 0.01$) and 7.6% ($p < 0.01$), respectively (Table I). The overall relative effects of the upright posture and exercise on platelet aggregability and fibrinolytic activity are summarized in Table I and Figure 3 (a and b).

DISCUSSION

This study clarifies several aspects of the changes in determinants of thrombus formation produced by assuming the upright posture, and exercise. It demonstrates that (1) assuming the upright posture in the morning produces a rapid surge in plasma catecholamine and renin activity levels that is accompanied by increased platelet aggregability; (2) the changes produced by the upright posture cease within 45 minutes after return to the supine position; (3) taking the upright posture later in the day produces changes similar to those produced in the morning; (4) the upright posture produces a moderate increase in fibrinolytic activity that tends to be less pronounced after 90 minutes in the upright position; (5) exercise does not increase platelet aggregability to a level higher than that caused by the upright posture but is associated with a significant increase in catecholamines, fibrinolytic activity and hematocrit value. Thus, the upright posture and exercise produce different profiles of changes in these determinants of thrombosis.

The demonstration in the present study that upright posture causes an increase in platelet aggregability (Figures 1 and 2, Table I) confirms previous reports of this phenomenon in normal subjects and in patients with coronary artery disease.[4,13] The present study adds new findings: This increase can be reversed by return to the supine position, and it can be reproduced by assuming upright posture at a later time of day.

The degree to which the increase in fibrinolytic activity associated with the upright posture modifies the overall thrombotic tendency of the blood is unknown, since it is not possible simply to add or subtract the results of the 2 processes. However, changes in platelet aggregation and fibrinolytic activity are homeostatic or autoregulatory, serving to maintain blood fluidity (Figures 2 and 3 [a and b]). It is uncertain whether patients

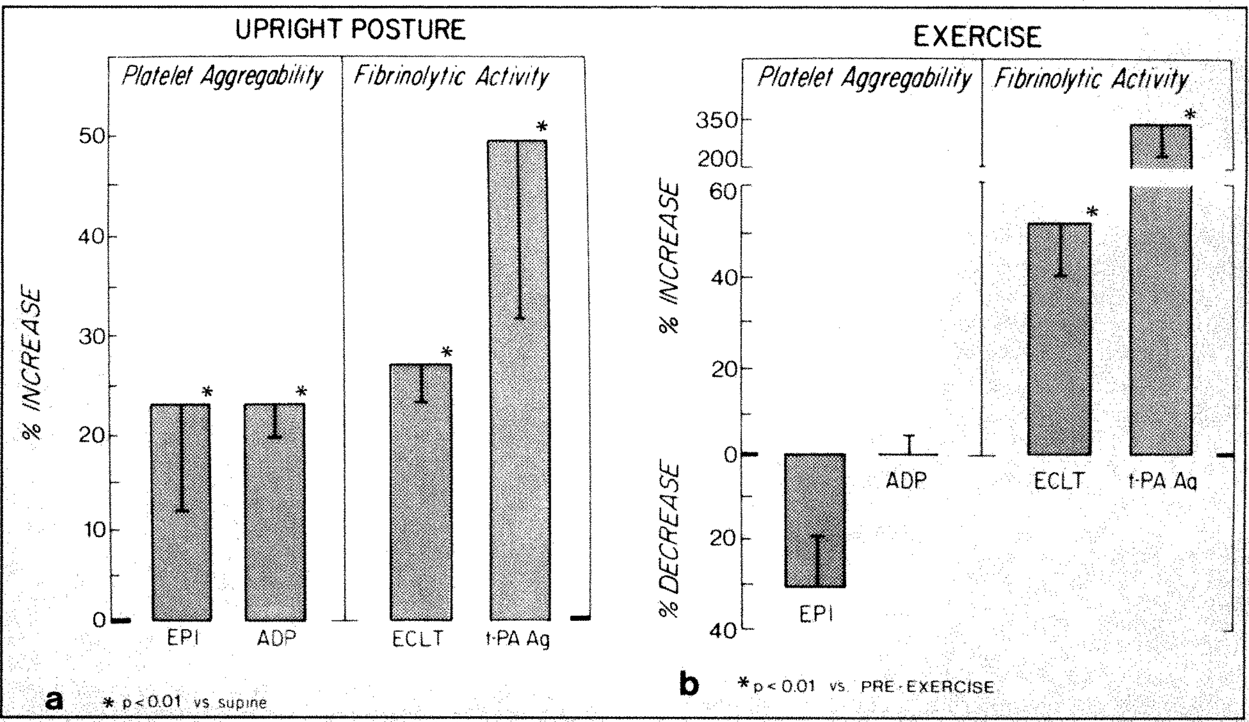

FIGURE 3. Relative overall effects of upright posture combining data from the morning and noon *(a)* and exercise *(b)* on adenosine diphosphate (ADP)- and epinephrine (EPI)-induced platelet aggregation, and fibrinolytic activity (estimated as euglobulin clot lysis time [ECLT] and tissue-type plasminogen activator antigen [t-PA Ag]).

with vascular disease, as opposed to normal subjects, demonstrate a similar antithrombotic fibrinolytic increase after assuming upright posture, since basal fibrinolytic activity has been reported to be decreased in patients with coronary artery disease.[14,15]

The failure of platelet aggregability to increase with strenuous exercise despite a five- to sixfold increase in plasma catecholamine levels is at variance with the previously reported association between platelet aggregability and even smaller plasma catecholamine increases.[3,13] It is possible that (1) the functional state of platelet adrenoceptors is down-regulated by high levels of catecholamine during exercise,[7,16] a change that may not be triggered by the relatively small catecholamine increase observed after the upright posture; (2) prostacyclin, a prostanoid which inhibits platelet aggregation, increases in plasma during exercise,[17] whereas the increase in prostacyclin during assumption of the upright posture may be more limited; and (3) the surge of tissue-type plasminogen activator observed during exercise may disaggregate platelets, as reported in vivo.[18] Although exercise does not produce an increase in platelet aggregability beyond that produced by the upright posture, it causes a significant increase in hematocrit that would increase whole blood viscosity. This tendency, which may increase the thrombotic potential, is countered by a marked increase in fibrinolytic activity (Figures 2 and 3 [a and b]).

The sum effect of these opposing changes on thrombotic potential, and how this balance is modified during different daily activities in patients with coronary artery disease, is uncertain.

These observations are of importance in light of a newly proposed hypothesis of the mechanism of triggering of coronary thrombosis.[19] It has been proposed that the process leading to coronary thrombosis begins when an external activity such as assuming the upright posture or exercise ruptures a vulnerable atherosclerotic plaque. Once the rupture occurs, the coagulability of the blood may determine whether a harmless mural thrombosis or life-threatening occlusive thrombus forms. The present study demonstrates that a stress such as near-maximal exercise, which could conceivably cause rupture of a vulnerable plaque owing to transient arterial hypertension, may also have a transient beneficial effect on blood coagulation, thereby delaying the onset of occlusive thrombosis. This possible scenario indicates the need for further characterization of the changes in the determinants of blood coagulation produced by activities that may trigger coronary artery thrombosis.

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Transesophageal Echocardiography to Assess Mitral Valve Function and Flow During Cardiopulmonary Resuscitation

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This study further defines the mechanism of blood flow during closed-chest compression using transesophageal Doppler echocardiography. Although the echocardiographic demonstration of mitral valve closure during closed-chest compression has been used as evidence of direct cardiac compression, mitral valve closure has also been documented to occur during resuscitation by selectively increasing intrathoracic pressure. Transesophageal Doppler echocardiography was used to assess mitral valve position and flow in 17 adult patients undergoing cardiopulmonary resuscitation with a mechanical piston compression device. Left and right ventricular fractional shortening, mitral valve position with chest compression, timing and magnitude of transmitral flow, and anteroposterior chest diameter were recorded. In 12 patients (group I), the mitral valve closed during the downstroke of chest compression; in the remaining 5 (group II), it opened further. Peak transmitral flow occurred during the release phase and was significantly higher ($p < 0.05$) in group I (39.5 ± 9.3 cm/s) than the peak flow in group II (21.3 ± 5.9 cm/s), which occurred during the downstroke of chest compression. Left ventricular fractional shortening inversely correlated ($r = -0.68$; $p = 0.02$) with the anteroposterior chest diameter, but did not correlate with peak transmitral flow ($r = 0.34$; p = not significant). It is concluded that the mitral valve closes during the downstroke of chest compression in most adult patients during resuscitation. The absence of a relation between mitral valve flow and left ventricular fractional shortening supports the hypothesis that other factors such as nonuniform increases in intrathoracic pressure cause the mitral valve to open or close during chest compression.

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The mechanisms of blood flow during closed-chest cardiopulmonary resuscitation (CPR) in humans have been debated since the technique was first described in 1960.[1-5] Two competing theories have been proposed to explain how blood circulates during CPR.[1-8] The cardiac pump theory proposes that direct cardiac compression (i.e., left ventricular) creates atrioventricular gradients that close the mitral valve during chest compression. An alternative, thoracic pump theory postulates that forward blood flow is achieved when increased intrathoracic pressure squeezes blood out of the heart and the great vessels, with prevention of retrograde flow by venous valves at the thoracic inlet. In this formulation, the heart was initially thought to act as a passive conduit, enabling the mitral valve to remain open during chest compression. The 2 mechanisms appeared to be distinguishable on the basis of whether the mitral valve is open or closed during the downstroke of chest compression, until Halperin et al[9] showed that mitral valve closure with concomitant retrograde pressure gradients can be produced by nonuniform increases in intrathoracic pressure without chest wall compression. This study assesses mitral valve position and flow during closed-chest resuscitation in humans, and their relation to left ventricular compression.

METHODS

The study group comprised a convenience sample of 20 adult patients who were admitted to the emergency department in cardiopulmonary arrest when portable, transesophageal echocardiographic instrumentation was available (8 A.M. to 8 P.M., Monday through Friday). The protocol excluded nonadults (aged <18 years), patients whose cardiac arrest was due to traumatic injury or terminal illness, and those in whom the transesophageal probe could not be inserted despite laryngoscopic guidance. The time from the onset of patient collapse until the call for assistance from a bystander was received at the 911 center was estimated by those who witnessed the arrest or by family members who had most recently seen the patient.

All patients were treated initially by paramedics, and had not had return of spontaneous circulation, using the American Heart Association protocols and procedures algorithm.[10] Conventional resuscitation procedures[10] including drug therapy and defibrillation, as clinically indicated, continued throughout the study period. Epinephrine was administered as either a 1 mg bolus every 5 minutes or a continuous infusion of 200 μg/min.

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TABLE I Echocardiographic and Doppler Findings During Standard Cardiopulmonary Resuscitation at a Force of 120 Pounds and a Compression Rate of 90 per Minute

	Timing of MV Flow	Rhythm	Peak TMF (cm/s)	TVI (sec)	LV Dimension (cm)	LV % FX Shortening	RV % FX Shortening	AP Diam. (cm)
Group I								
1	Release	Asystole	35.0	6.5	3.5	20	70	
2	Release	EMD	40.4	5.9	3.6	14	88	
3	Release	VT/VF	31.9	4.9	3.8	29	58	
4	Release	Asystole	31.6	5.4	4.3	28	45	
5	Release	Asystole	65.2	7.7	2.2	41	82	18
6	Release	Asystole	35.0	4.3	4.0	40	62	19
7	Release	VT/VF	32.5	5.5	3.9	33	44	19
8	Release	VT/VF	40.9	7.1	4.3	14	56	24
9	Release	EMD	39.8	3.9	1.9	32	44	22
10	Release	VT/VF	30.4	2.4	3.0	20	40	23
11	Release	VT/VF	44.0	6.3	5.0	15	70	20
12	Release	VT/VF	46.9	3.2	5.0	26	74	23
No.			12	12	12	12	12	8
Mean			39.5	5.3	3.7	26	61	21
SD			9.3	1.5	0.9	9	15	2
Group II								
1	Compression	VT/VF	16.1	2.8	3.8	12	38	
2	Compression	Asystole	31.6	3.2	2.4	38	52	
3	Compression	VT/VF	15.7	2.5	3.1	19	56	27
4	Compression	VT/VF	23.5	4.2	4.5	31	54	22
5	Compression	EMD	19.6	2.1	4.9	20	26	23
No.			5	5	5	5	5	3
Mean			21.3	3.0	3.7	24	45	24
SD			5.9	0.7	0.9	9	11	2

AP Diam. = anterior to posterior chest diameter; EMD = electromechanical dissociation; FX = fractional; LV = left ventricular; MV = mitral valve; RV = right ventricular; TMF = transmitral flow; TVI = time-velocity integral; VT/VF = ventricular tachycardia/fibrillation.

CPR was performed in all patients with a Model 1013 programmable mechanical piston compression device (Michigan Instruments, Inc., Grand Rapids, Michigan) that was set at a rate of 90 compressions per minute using 120-pound force of pressure. Fifty percent of each duty cycle was spent on the downstroke; the remainder was spent on the upstroke. The piston time constant was 90 ms. Twelve ventilations per minute (each lasting 1.5 second) were delivered in a 5:1 compression-to-ventilation ratio with a peak inspiratory pressure of 45 cm of water and a maximal flow rate of 140 liters/min. The ventilator delivered an oxygen concentration of 0.8.

After confirmation of endotracheal intubation, a 5 MHz transesophageal probe was inserted in the distal esophagus. Basal 4-chamber echocardiographic views and transgastric short-axis images were obtained using a Sonos 1000 Model 77020AC echocardiographic unit (Hewlett-Packard, Andover, Massachusetts). Measurements of left and right ventricular fractional shortening were defined as the percent difference in maximal (immediately beneath the level of the atrioventricular valve leaflet tips before compression) and minimal chamber dimensions at the same level after compression divided by maximal chamber dimension. Chamber dimensions were obtained from either the basal long-axis or transgastric short-axis view, depending on which was optimal. The average of 5 peak transmitral velocities and time-velocity integrals were assessed using pulsed-wave Doppler in the basal long-axis view with the sampling volume positioned at the tip of the mitral valve leaflets. In the last 12 patients studied, the anterioposterior chest diameter was measured as the distance from the lower third of the sternum to the backboard. In 8 patients, mitral valve position and flow were recorded using piston compression force at 30-, 60-, 90- and 120-pound force. At each force, a standard compression velocity and high-acceleration compression were delivered to assess the impact of a shorter time to peak compression force on transmitral flow timing and magnitude.

Ethical considerations: Transesophageal echocardiographic recordings were obtained while the chest compression technique was experimentally varied as part of an ongoing resuscitation protocol approved by the committee on the conduct of human research at Virginia Commonwealth University.

Statistical analysis: Patients were divided into 2 groups based on whether the mitral valve closed (group I) or opened further (group II) during the downstroke of chest compression. Anatomic and Doppler values for the 2 groups were compared using unpaired *t* testing. The Wilcoxon rank sum test was used to compare time intervals from the onset of patient collapse to the initiation of CPR between groups. A p value <0.05 was considered statistically significant. A Pearson correlation coefficient was used to compare left ventricular fractional shortening and transmitral flow with anteroposterior chest diameter.

RESULTS

Patient characteristics: The study group comprised 20 patients in whom transesophageal echocardiography was performed within 5 minutes of arrival at the emergency department. Of these 20 patients, consistent parallel alignment of the pulsed Doppler sampling beam at the tip of the mitral valve leaflets throughout the compression and release cycle could be obtained in 17. Because most patients did not survive, clinical information could be obtained in only 11. Mean age was 63 ± 9 years. Three patients had known coronary artery disease, 1 had systemic hypertension, and 1 had an unexplained cardiomyopathy. One patient had a recent type I aortic dissection, 2 had chronic obstructive pulmonary disease, 1 had human immunodeficiency virus-related liver failure, 1 had a recent cerebrovascular accident, and 1 had recently abused cocaine. The median times that elapsed before the arrival of basic life support were 2 minutes (range 1 to 13) in group I and 6 minutes (range 1 to 25) in group II ($p = 0.18$). Return of a spontaneous rhythm occurred in only 3 patients; all 3 had mitral valve closure with chest compression.

Echocardiography: Transmitral Doppler flow profiles, left ventricular dimensions, and left and right ventricular fractional shortening are listed in Table I. In 12 patients (group I), the mitral valve closed during the downstroke of chest compression; in the remaining 5 (group II), it remained open or opened further (Figure 1). There was no significant difference in left ventricular fractional shortening between groups (group I 26 ± 9% vs group II 24 ± 9%; p = not significant). Right ventricular fractional shortening averaged 61 ± 15% (range 40 to 88) for group I, and 45 ± 11% (range 26 to 54) for group II ($p = 0.08$). Left ventricular fractional shortening in all patients was significantly less than was right ventricular fractional shortening. Despite the use of a backboard, the left ventricle was displaced posteriorly with the downstroke of chest compression in all patients.

Mitral valve position and motion depended only on the phase of the chest compression in patients with asystole. However, patients who were in ventricular fibrillation or tachycardia had undulating or fluttering mitral valve motions independent of chest compression. This high-frequency, low-amplitude mitral valve motion did not interfere with the determination of when forward flow occurred using Doppler. In 1 patient with an organized rhythm without a pulse, there was anatomic and Doppler evidence of transmitral flow independent of chest compression.

Peak transmitral flow was observed during the release phase in group I and during compression in group II. Peak transmitral flow was significantly higher ($p < 0.05$) in group I (39.5 ± 9.3 cm/s) than the peak flow in group II (21.3 ± 5.9 cm/s), which occurred during the downstroke of chest compression. Time-velocity integrals were also significantly higher in group I (Table I). Both groups were similar with respect to maximal end-diastolic, left ventricular dimensions before each compression (group I 3.7 ± 0.9 cm vs group II 3.7 ± 0.8 cm; $p = 0.80$) and to degree of left ventricular fractional shortening (group I 26 ± 9% vs group II 24 ± 9%; $p = 0.99$). Color Doppler examination was performed in 8 group I and 4 group II patients. There was a small regurgitant color jet observed during chest compression in 7 group I patients, but none in group II.

Eight of eleven patients in whom the anteroposterior diameter was recorded were in group I, and 3 were in group II. Left ventricular fractional shortening inversely

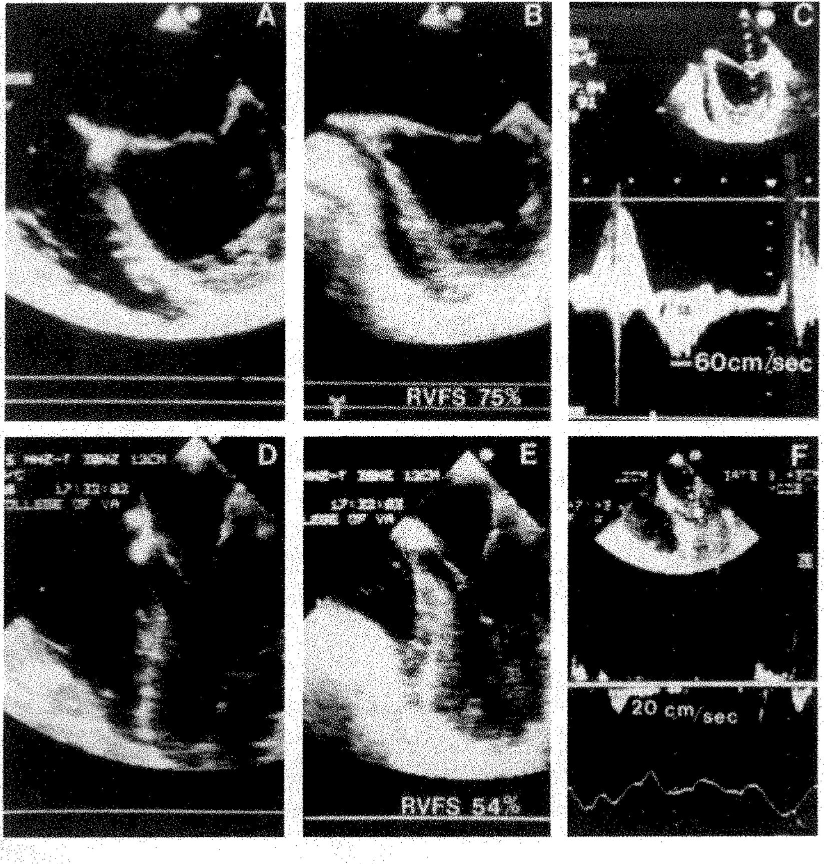

FIGURE 1. Transesophageal echocardiographic images and transmitral Doppler flow profiles from patient who had mitral valve closure with chest compression during cardiopulmonary resuscitation *(A to C)*, and from another whose mitral valve remained open with chest compression *(D to E)*. *A and D*, before chest compression with mechanical piston, and *B and E*, maximal piston compression. As can be seen from pulsed Doppler, peak velocity (during release phase) from patient who had mitral valve closure with chest compression was almost 60 cm/s, whereas maximal transmitral velocity from patient with open mitral valve (during chest compression) was 20 cm/s. RVFS = right ventricular fractional shortening.

correlated with anteroposterior chest diameter in all patients ($r = -0.68$; $p = 0.02$). There was also a weak negative correlation between anteroposterior chest diameter and peak transmitral flow ($r = -0.61$; $p < 0.05$). However, there was no correlation between peak transmitral flow and left ventricular fractional shortening ($r = 0.34$; p = not significant).

In 8 patients (5 in group I and 3 in group II), compression force was decreased to 90-, 60- and 30-pound force. Whereas all patients in group II continued to demonstrate mitral valve opening, 1 of the 4 patients at the 60-pound force and 3 at the 30-pound force in group I did not demonstrate mitral valve closure with chest compression. Two group I patients who did not demonstrate mitral valve closure at the 30-pound force also lost forward transmitral flow during the release phase of CPR.

When high-acceleration compression was used at a force of 120 pounds, 2 patients who had an open mitral valve position with chest compression (group II) demonstrated transmitral flow during the release phase of CPR. However, there was no evidence of mitral valve closure with chest compression in any group II patient with high-acceleration piston force.

DISCUSSION

The major findings of this study are as follows: (1) In most patients receiving closed-chest CPR, the mitral valve closes with chest compression, and (2) maximal transmitral Doppler flow occurs in the group with mitral valve closure during chest compression. Transthoracic 2-dimensional echocardiography has been used to demonstrate mitral valve position during closed-chest compression in animals[2,8–9,11] and in a small number of humans,[4] but the technique is limited by motion artifact. Feneley et al[8] demonstrated that the mitral valve closes in dogs when high-velocity manual chest compressions generate left ventriculoatrial pressure gradients >38 mm Hg or when pneumatic-piston compressions generate peak left ventricular pressures >40 mm Hg. When weaker compression force is used, the mitral valve remains open. In 2 separate studies[4,12] involving a total of 9 patients, manual chest compression appeared to open the mitral valve on transthoracic echocardiography.

Transesophageal echocardiography improves the visualization of the left atrium, mitral valve and left ventricle during manual CPR.[13] However, early observations also differed concerning the position of the mitral valve during chest compression.[14,15] Higano et al[14] reported that the mitral valve closed with manual chest compression and opened during release in 2 adult humans. In contrast, Wright[15] reported that the mitral valve stays open throughout chest compression based on observations in 4 cases imaged with biplane transesophageal echocardiography.

In the present study, most patients had mitral valve closure with chest compression. One explanation for this is that we used a higher compression force (120 pounds) than what is presently recommended. We could no longer consistently demonstrate mitral valve closure in a subset of patients in group I when the compression force was reduced to 60 pounds. In animals, the demonstration of mitral valve closure also seems dependent on compression force. There is a significant increase in echocardiographic evidence of mitral valve closure and improved forward flow in pigs when the chest compression force is increased from 350 to 500 Newtons.[16] Therefore, the compression force may be important in determining the magnitude of the left ventriculoatrial gradient responsible for mitral valve closure.

We observed no relation between the incidence of mitral valve closure and the amount of left ventricular fractional shortening during chest compression. This supports the hypothesis that other factors independent of direct left ventricular compression cause the mitral valve to open or close during chest compression. Halperin et al[9] observed in animals that mitral valve closure by echocardiography could be achieved with balloon inflation of the thoracic cavity sufficient to cause lung deflation; thus, they demonstrated that left ventriculoatrial gradients could be produced without chest wall or left ventricular compression. Furthermore, there is echocardiographic evidence in humans that the left ventricle may actually increase in diameter in some regions during chest compression despite mitral valve closure. Lanfranconi et al[17] observed with transesophageal echocardiography in 5 patients that chest compression was accompanied by mitral valve closure. This was accompanied, however, by increased left ventricular lateral and decreased anteroposterior diameter.

We also demonstrated a smaller group of 5 patients in this study (group II) who did not have mitral valve closure with chest compression. This group demonstrated forward transmitral flow during the compression phase of CPR. There are several potential mechanisms for this finding. Although the chest compression force was constant during this study, it is possible that the increase in intrathoracic pressure in these patients did not exceed the pressure in the pulmonary circulation during chest compression, and thus a left ventriculoatrial gradient of sufficient magnitude to close the mitral valve did not occur. Furthermore, it is possible that the compression force in these patients was not applied directly over the heart. Feneley et al[8] observed in animals that the mitral valve did not close when the compression force was applied to regions of the chest wall that were not overlying the heart. In addition, they also noted that low-velocity compressions did not close the mitral valve. We noted in 2 patients in group II that higher acceleration compression force could induce forward transmitral flow during the release phase of CPR. This forward flow was not accompanied by mitral valve closure or Doppler evidence of mitral regurgitation during chest compression.

Peak transmitral flow velocity and time-velocity integrals were higher when the mitral valve closed with chest compression. As with the incidence of mitral valve closure, these flow parameters did not correlate with the amount of left ventricular fractional shortening. The higher peak velocity and time-velocity integral occurred during the release phase, whereas patients with a persistent open mitral valve during chest compression had forward flow only during compression. This may explain the echocardiographic and hemodynamic data in animals, which demonstrate that myocardial and cerebral perfusion are enhanced when the mitral valve closes during chest compression.[16] The mechanism for the ventriculoatrial gradients responsible for the increased transmitral flow remains unclear. The absence of a correlation between direct left ventricular compression and peak transmitral flow in this study supports the hypothesis that other factors may produce the gradient, such as nonuniform increases in intrathoracic pressure.[9]

Study limitations: Although this study provides unique information concerning mitral valve function and flow, simultaneous assessments of hemodynamic data and degree of sternal compression were not obtained. Assessment of right atrial, pulmonary artery, aortic and esophageal pressures would supplement the information obtained with Doppler. Furthermore, the depth of chest compression may have varied between patients, despite the same force of compression.

Moreover, the absence of a correlation between single-plane left ventricular fractional shortening and transmitral flow velocity does not completely rule out that direct compression contributes to forward flow. The single-plane methods we used are unable to determine the 3-dimensional changes in the left ventricle that occur with CPR. However, our findings are supported by other investigators who have used multiple imaging planes and shown no net change in left ventricular dimensions during standard CPR. Feneley et al[8] and Lanfranconi et al[17] have demonstrated that sternal compressions result in increases in chamber dimensions in 1 view and in decreases in another. These echocardiographic findings support the finding that direct left ventricular compression does not have a role in forward flow during CPR.

Finally, we observed significant differences in transmitral velocity and not in volume between the 2 groups. Furthermore, Doppler sampling at the mitral annulus (instead of mitral leaflet tips) would be a better approximation of volume flow across the valve. However, we also measured time-velocity integrals, which are better than peak velocity in determining the amount of flow, and found they were also significantly greater in group I.

Clinical implications: This study reveals that transesophageal echocardiography can provide immediate anatomic and functional information during CPR. The finding that mitral valve closure during closed chest compression is associated with a significantly greater peak transmitral velocity is the first demonstration in humans that closure of this valve may be associated with higher flow rates. However, because we obtained the data in patients who did not survive prehospital resuscitation, we had very few survivors. Only 3 of 12 patients who demonstrated mitral valve closure with chest compression survived the resuscitation, whereas none of 5 with a persistent open mitral valve position survived. However, this survival difference may indicate that mitral valve closure with chest compression may represent not only a group of patients with improved forward flow, but better clinical outcome as well. To demonstrate that mitral valve closure during chest compression is an important factor in determining the outcome of resuscitation, large numbers of patients should be studied earlier during resuscitation (such as in critical care settings). Recent advances in the design of the ultrasound probes will also add to the information obtained. With biplane transesophageal echocardiography, more imaging planes of the left ventricle during chest compression can be obtained, and Doppler assessment of left ventricular outflow tract may be possible.[18]

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Arrhythmias After Cardiac Transplantation

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The etiology and clinical significance of sustained arrhythmias, and atrial and ventricular premature complexes (APCs and VPCs, respectively) after heart transplantation are controversial. Fifty adult recipients surviving >2 weeks were studied by continuous telemetry while in the hospital and by ambulatory electrocardiographic monitoring at 2, 4, 6, 12 and 24 weeks after transplantation. The median APC frequency was greater among subjects who experienced allograft rejection in the early postoperative period (0.7/hour, range 0 to 23) than among those who did not (0.2/hour, range 0 to 10.4) ($p = 0.04$). The APC frequency in all subjects decreased from 0.25/hour (range 0 to 23) early to 0/hour (0 to 14) later ($p = 0.04$). Atrial flutter was the most frequent sustained arrhythmia; it was recorded in 5 of 21 rejectors and in 1 of 29 nonrejectors ($p = 0.04$), and 11 of 16 episodes (69%) were related to acute rejection temporally. VPCs were recorded in all patients early after transplantation, but the median frequency subsequently decreased from 4.6/hour (range 0.5 to 470) early to 1.25/hour (range 0 to 225) later ($p < 0.001$). VPC frequency was unrelated to rejection. Sustained ventricular tachycardia was recorded once and was caused by the proarrhythmic effect of flecainide.

Thus, APCs and VPCs occur frequently after transplantation. Frequent APCs are associated with rejection, whereas the main determinant of VPC frequency is time after transplantation. Atrial flutter is closely associated with rejection and should be regarded as an indication for endomyocardial biopsy. Ventricular tachycardia occurs seldom, and in this study was due to proarrhythmic drug effects.

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The transplanted human heart is exposed to injury both from cold ischemia during organ procurement and subsequently from allograft rejection. The arrhythmogenic potential of these processes has been suspected for some time, but results of previous studies were contradictory. Associations between atrial arrhythmias and allograft rejection have been reported by some investigators[1,2] but the finding has not been universal.[3] Prolonged ischemic time has been associated with both an increased frequency of arrhythmias in general[3] and specifically bradyarrhythmias due to sinus node dysfunction.[4] Previous studies all had significant limitations; many included patients transplanted before cyclosporine immunosuppression became available[1,3,5] and their relevance to current transplantation practice is therefore open to question. Data collection methods have often been inadequate,[1,3,4] relying on 12-lead electrocardiograms and hospital telemetry, with the potential for bias toward patients with complications. This is the first prospective study of arrhythmias in a large number of heart transplant recipients using 24-hour ambulatory monitoring in addition to telemetry data. Bradyarrhythmias are very frequent in the immediate postoperative period.[6] The protocol for this study was designed primarily to assess the frequency and significance of atrial and ventricular premature complexes (APCs and VPCs, respectively) and tachyarrhythmias after the immediate postoperative period.

METHODS

Fifty consecutive adult transplant recipients were studied. Patients surviving <2 weeks after transplantation were excluded from the study. The operative technique was standard.[7] Immunosuppression was achieved with cyclosporine, azathioprine and prednisolone (maintenance dose of 0.2 mg/kg).

Definitions: Atrial arrhythmias were defined as sustained if they persisted for >1 hour or caused hemodynamic disturbance. Ventricular tachycardia was defined as >3 ventricular complexes in sequence at a rate of >100 beats/min; it was sustained if it persisted for >30 seconds or caused hemodynamic disturbance. Early arrhythmias were defined as occurring ≤6 weeks after transplantation. Late arrhythmias refer to those occurring between the sixth postoperative week and 6 months.

A "rejector" was defined as a subject who had ≥1 episode of rejection of "moderate" or greater severity, according to the Billingham classification.[8]

Telemetry: All patients were monitored by continuous telemetry while in the hospital, and any sustained arrhythmias were recorded.

Ambulatory monitoring and analysis: Twenty-four hour ambulatory electrocardiographic monitoring was performed at 2, 4, 6, 12 and 24 weeks after transplantation using the Reynolds Medical "Tracker" system. Re-

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TABLE I Incidence of Arrhythmias

Arrhythmia	No. of Patients (%)
Atrial premature complexes	31 (62)
Nonsustained supraventricular tachycardia	9 (18)
Atrial flutter	6 (12)
Atrial fibrillation	3 (6)
Ventricular premature complxes	50 (100)
Couplets	47 (94)
Triplet	29 (58)
Nonsustained ventricular tachycardia	23 (46)
Sustained ventricular tachycardia	1 (2)

cordings were analysed using a Reynolds Medical Pathfinder 3. The frequency of atrial and ventricular premature beats were determined by the analyzer. The accuracy of automated ectopic counts were assessed by 2-minute sample printouts during each hour of monitoring. Tapes that were of insufficient quality to produce accurate counts were excluded from analysis. Arrhythmias recorded during an endomyocardial biopsy procedure were excluded. Nonsustained arrhythmias and ectopic activity were assessed only from ambulatory monitoring data.

Clinical variables analyzed: Possible associations between all types of arrhythmias, perioperative ischemic time and donor age were examined. The relation between arrhythmias and allograft rejection was examined by both comparisons between rejectors and nonrejectors, and assessment of the frequency of arrhythmias during acute rejection episodes.

Statistical analysis: Statistical comparisons were performed using the Wilcoxon sign rank test, Mann-Whitney U test, Fisher's exact test, chi-square test and linear regression analysis. Where the distribution of data is heavily skewed, median values and ranges are presented; means and SD are used elsewhere.

RESULTS

Four subjects died during the study period. In all, 239 of a possible 250 recordings were available. Of these recordings, 208 (88%) were suitable for full analysis, representing 4,992 hours of ambulatory monitoring in 50 patients.

Table I summarizes the incidence of each arrhythmia occurring in the study population. All sustained arrhythmias were recorded during hospital telemetry, with the exception of 1 episode of atrial flutter recorded during ambulatory monitoring. One subject with frequent ventricular ectopic activity complained of intermittent palpitations throughout each period of ambulatory monitoring. No other patient reported symptoms during any recording.

The mean ischemic time was 168 ± 49 minutes, and the donor age was 32 ± 11 years. Twenty-one of 50 subjects (42%) were rejectors, and 29 (58%) were nonrejectors. Sixteen of 86 recordings (19%) in the rejector group were obtained during an episode of biopsy-proved moderate rejection. One episode of severe rejection occurred during the study period and was associated with an asystolic cardiac arrest from which the patient was successfully resuscitated.

Atrial premature complexes: APCs were recorded in 31 of 50 subjects (62%) early after transplantation and in 19 of 43 (44%) later. The median (range) frequency decreased from 0.25/hour (0 to 23) early after transplantation to 0/hour (0 to 14) later ($p = 0.04$). APCs were significantly more frequent in rejectors (0.7/hour, 0 to 23) than in nonrejectors (0.2/hour, 0 to 10.4) early after transplantation ($p = 0.04$). There was a similar trend later, but it was not statistically significant. A higher frequency of APCs was also recorded during moderate rejection episodes (0.5/hour [0 to 62] vs 0/hour [0 to 23]) than during other recordings, but this difference did not achieve statistical significance. Regression analysis revealed no association between APC frequency and either donor age or operative ischemic time.

Nonsustained atrial fibrillation and tachycardia: Nonsustained atrial tachycardia was recorded in 9 of 50 subjects (18%). There was no significant change in its median frequency with time after transplantation (0 episode/24 hours [range 0 to 30] early vs 0 [0 to 1] later). Nonsustained atrial arrhythmias were not associated with rejection; they were recorded in 4 of 21 rejectors and in 5 of 29 nonrejectors.

Sustained atrial arrhythmias: Sustained atrial arrhythmias were recorded in 9 patients (18%); 6 (12%) had atrial flutter and 3 (6%) had atrial fibrillation. All sustained atrial arrhythmias occurred within the first 6 weeks after transplantation.

Atrial flutter was recorded in 5 of 21 rejectors (24%) compared with in only 1 of 29 nonrejectors (3%) ($p = 0.04$). Eleven of 16 episodes were temporally related (≤72 hours) to biopsy-proved rejection. Two episodes in 1 patient occurred during a course of total lymphoid irradiation for intractable rejection. Six of 16 episodes resolved spontaneously, 9 were treated by overdrive atrial pacing at the time of endomyocardial biopsy (successful in 7), and 3 needed direct-current cardioversion. Two patients received drug treatment (1 with digoxin only, and the other sequentially with disopyramide, flecainide and amiodarone).

One episode of atrial fibrillation was recorded in 2 of 21 rejectors; both were temporally related to biopsy-proved rejection. The other nonrejecting subject had 7 episodes of atrial fibrillation. This subject had evidence of significant systolic dysfunction of the transplanted heart (ejection fraction 25%), with electrocardiographic evidence of left bundle branch block and frequent VPCs. This suggests poor organ preservation at the time of transplantation, and a different potential mechanism for the atrial fibrillation.

Ventricular premature complexes: VPCs were recorded in all 50 subjects early after transplantation and in 42 of 44 (95%) later. The median (range) VPC frequency decreased from 4.6/hour (0.5 to 470) early after transplantation to 1.25/hour (0 to 225) later ($p < 0.0001$). There were no significant differences in median VPC frequency between rejectors (6.1/hour, 1.1 to 470) and nonrejectors (3.7/hour, 0.5 to 139) or between recordings obtained during rejection episodes (1.8/hour, 0.5 to 14.2) and at other times (3.2/hour, 0 to 80).

Complex ventricular premature complexes and nonsustained ventricular tachycardia: Complex VPCs (couplets and triplets) and nonsustained ventricular tachycardia were recorded in 47 of 50 subjects (94%) early after transplantation and in 24 of 44 (55%) later. The frequencies of couplets, triplets and nonsustained ventricular tachycardia were higher early after transplantation than later (4/24 hours [0 to 154] vs 0.5/24 hours [0 to 347], 0.5/24 hours [0 to 56] vs 0/24 hours [0 to 11], and 0/24 hours [0 to 15] vs 0/24 hours [0 to 2], respectively; $p < 0.001$). There were no associations between complex VPCs, nonsustained ventricular tachycardia and rejection. Regression analysis did not identify any relation between these arrhythmias and donor age or operative ischemic time.

Sustained ventricular tachycardia: Sustained ventricular tachycardia was observed on 1 occasion only and was treated by direct-current cardioversion. This episode was not related to rejection, but to therapy with flecainide for prophylaxis of recurrent atrial flutter. Ventricular tachycardia did not recur after withdrawal of flecainide; thus it was considered a proarrhythmic effect of the drug.

DISCUSSION

Atrial arrhythmias: This is the first study to measure APC frequency systematically in transplant recipients using ambulatory electrocardiographic monitoring. We confirmed the previously reported[1,2] association between allograft rejection and atrial arrhythmias. In particular, sustained atrial flutter occurred almost exclusively in rejectors and was temporally associated with rejection in 11 of 16 cases. These results are very similar to those of Berke et al[1] who reported that 7 of 10 episodes of atrial flutter were associated with acute rejection episodes. We suspect a similar association with atrial fibrillation, although the number of episodes recorded was not sufficient to confirm this hypothesis. However, our results contrast with other recent studies in cyclosporine-treated patients,[3,4] which found no association between atrial arrhythmias and rejection. Little et al[3] reported a lower incidence of atrial arrhythmias in cyclosporine-treated subjects than in those receiving less effective immunosuppression. That analysis was confined to rejecting and nonrejecting groups, with no attempt to link rejection episodes with arrhythmias temporally. The study by Jacquet et al[4] was limited by very few sustained arrhythmia episodes; only 2 patients had sustained atrial arrhythmias, and 1 of these had 2 episodes of severe rejection.

The etiology of atrial arrhythmias during rejection episodes is unclear. Evidence from animal studies suggests that during allograft rejection, conduction impairment occurs only within the atrial myocardium.[9] Because of the patchy nature of the rejection process, the formation of macroreentrant circuits may result. Reduced ventricular compliance during rejection episodes[10] may cause changes in atrial hemodynamics and be potentially arrhythmogenic.

Ventricular arrhythmias: We confirmed the findings of recent studies[3,4] that ventricular premature beats, couplets, triplets and nonsustained ventricular tachycardia occur frequently early after transplantation and that the frequency decreases markedly with time. We did not find any association between these arrhythmias and prolonged ischemic time or advanced donor age. As in other recent studies,[3,4] ventricular arrhythmias were not associated with rejection.

Sustained ventricular tachycardia was not previously reported in transplant recipients, even those with advanced graft coronary artery disease.[5] Ventricular fibrillation was previously associated with severe rejection,[1] but in our patients the rarity of severe rejection precludes analysis of arrhythmias in this setting.

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A New Technique for Simultaneous Monitoring of Electrocardiogram and Walking Cadence

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A new technique for simultaneously recording continuous electrocardiographic (ECG) data and walking step rate (cadence) is described. The ECG and gait signals are recorded on 2 channels of an ambulatory Holter monitor. Footfall is detected using ultrathin, force-sensitive foot switches and is frequency modulated. The footfall signal provides an indication of the subject's activity (walking or standing), as well as the instantaneous walking rate. Twenty-three young and elderly subjects were studied to demonstrate the use of this ECG and gait recorder. High-quality gait signals were obtained in all subjects, and the effects of walking on the electrocardiogram were assessed. Initial investigation revealed the following findings: (1) Although walking rates were similar in young and elderly subjects, the elderly had both decreased heart rate (HR) variability ($p < 0.005$) and increased cadence variability ($p < 0.0001$). (2) Overall, there was an inverse relation between HR and cadence variability ($r = -0.73$). Three elderly subjects with no known cardiac disease had HR and cadence variability similar to those of the young, whereas elderly subjects with history of congestive heart failure were among those with the lowest HR variability and the highest cadence variability. (3) Low-frequency ($\cong 0.1$ Hz) HR oscillations (frequently observed during standing) persisted during walking in all young subjects. (4) In some subjects, both step rate and HR oscillated at the same low frequency ($\cong 0.1$ Hz) previously identified with autonomic control of the baroreflex. The modified Holter monitor enabled enhanced evaluation of the relation between the electrocardiogram and walking; it should augment assessment of conventional ECG measures, because changes in HR, ischemia, arrhythmias and HR variability can now be correlated with physical activity.

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We describe a new technique for simultaneously recording continuous walking rate and the electrocardiogram (ECG). Using a modified Holter monitor and ultrathin, force-sensitive foot switches, we can quantitatively relate beat-to-beat changes in the ECG to physical activity. This augments assessment of conventional electrocardiographic measures, because changes in heart rate (HR), ischemia, rhythm and HR variability can be correlated with physical activity. To demonstrate the use of the modified Holter monitor and its ability to augment interpretation of changes in the ECG, we studied 23 young and elderly subjects during periods of supine rest and walking and assessed the effects of walking on the ECG.

Simultaneous recording of the ECG and footfall also provides a unique means for assessing beat-to-beat changes in HR. HR variability has been studied widely, because it provides a noninvasive window into autonomic nervous system function and because reduced HR variability has been associated with congestive heart failure, coronary artery disease, aging and mortality in patients after myocardial infarction.[1-7] The modified Holter facilitates correlation of HR variability with gait dynamics and physical activity, thus providing further insight into HR variability, autonomic nervous system function and pathology. Assessment of the relation between variations in HR and step rate (cadence) was performed in 23 subjects to show how the modified Holter monitor may be used to study functional conditions and the related effects of age, disease and cadence variability on HR dynamics.

METHODS

Electrocardiogram and walking cadence monitoring: The ECG and cadence are recorded simultaneously and continuously on a 2-channel ambulatory recorder (model 455b, Del Mar Avionics, Irvine, California). Footfall is detected using ultrathin (<0.05 inch), force-sensitive switches (part 154, Interlink Electronics, Carpinteria, California) taped underneath each shoe. When the foot makes contact with the ground and applies force to the switch, the switch is activated. When the foot leaves the ground during the swing phase of gait, the switch is turned off. The on-off pattern provides an indication of a subject's activity (e.g., walking or standing), as well as the rate at which it is performed.

The recorder we use has 2 channels, 1 of which is used for the ECG. To record the activity of both feet (2 signals) on the other channel, the footfall signal is connected to a small, battery-powered interface circuit that produces the signal for recording. This interface takes as input the 2 foot switches (4 combinations of on-off states), and using frequency modulation, it generates a sine wave at 1 of 4 frequencies, depending on the state

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of the foot switches (Figure 1). This method enables us to establish unique states for supine resting, standing and walking. A detailed schematic of the circuit is available from the authors.

The recorded signals are played back on a Del Mar Avionics Electrocardioscanner (model 655) and digitized at 416 Hz/channel. After playback, the footfall signal is decoded by determining which of the 4 sine-wave frequencies is present at any given time. Because the correspondence between frequency and foot switch state is known (Figure 1), determination of the frequency establishes the state of each foot switch. The original on-off footfall pattern then reemerges (Figure 2). The footfall signal is automatically analyzed by a computer program that marks the beginning of each step by locating the time the decoded footfall signal goes from off to on (Figure 2). Each beat of the ECG is also identified and classified (annotated) using an automated arrhythmia detector.[8] Computer results are reviewed manually and edited as necessary. HR and cadence (steps/min) are then calculated by taking the reciprocal of the RR interval and step duration. Evenly sampled, instantaneous HR and cadence were obtained for spectral analysis by resampling the interbeat and interstep intervals at 2 Hz.

Subjects: Twenty-three subjects were recruited to participate in this pilot study. Subjects were divided into young and elderly groups. All subjects were living independently in the community and participating in normal activities of daily living. Selection criteria included no

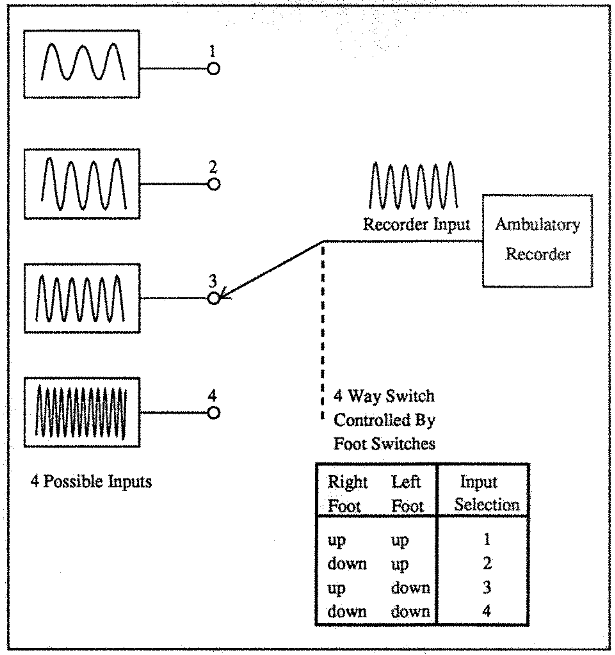


FIGURE 1. Functional block diagram showing how foot switches control input to recorder. Four frequencies are used to differentiate between standing (both switches on), standing on right foot only (right foot switch on), standing on left foot only (left foot switch on), and supine (no foot support, and neither switch is on). Voltage-controlled oscillator with 2 binary inputs encodes 4 combinations of 2 on-off switch states as 4 distinct frequencies and acts as 4-way switch.

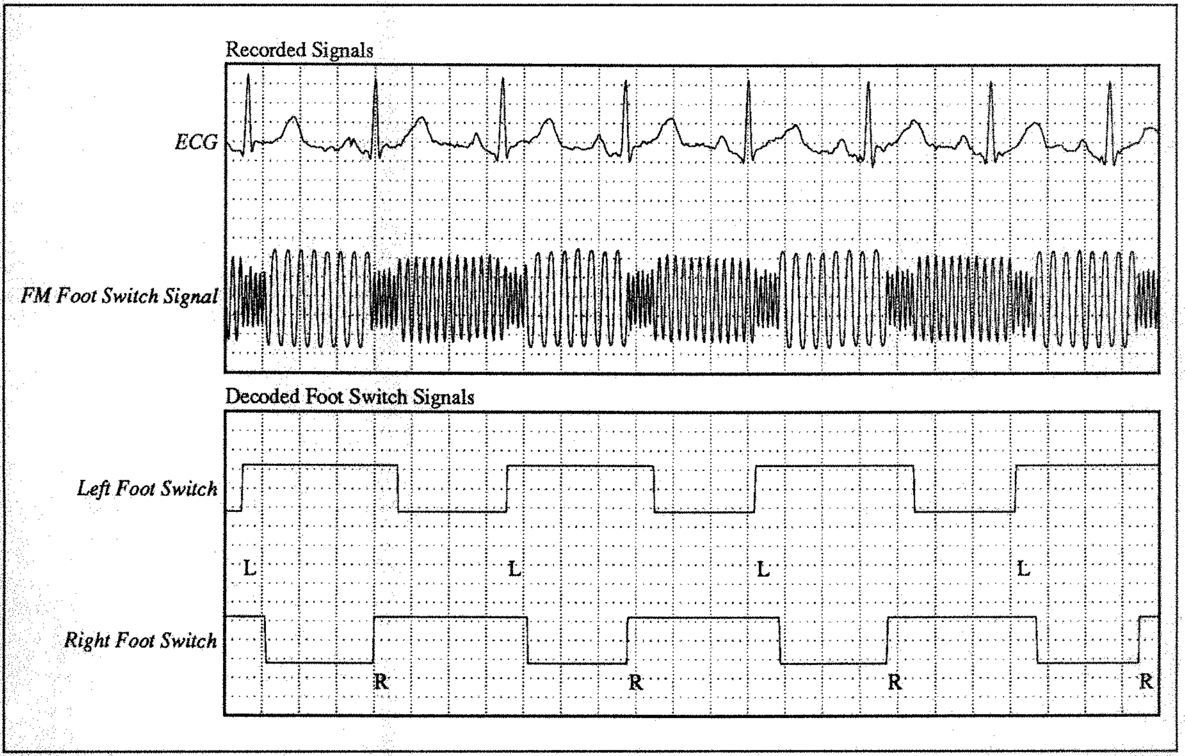


FIGURE 2. Electrocardiogram (ECG) and footfall signals during 5 seconds of walking after playback and digitization *(top)* and after decoding *(bottom)*. Three frequencies can be observed in frequency-modulated (FM) signal corresponding to 3 different foot switch states. Fourth frequency, which occurs when neither switch is activated, is not seen during this walking sequence because 1 foot was always in contact with ground. When foot switch is activated during stance, decoded signal goes from low to high, as seen in decoded foot switch signals. *Annotations* corresponding to beginning of right and left foot stance are displayed and marked with Rs and Ls, respectively. Each frequency corresponds to different combination of on-off foot switch states.

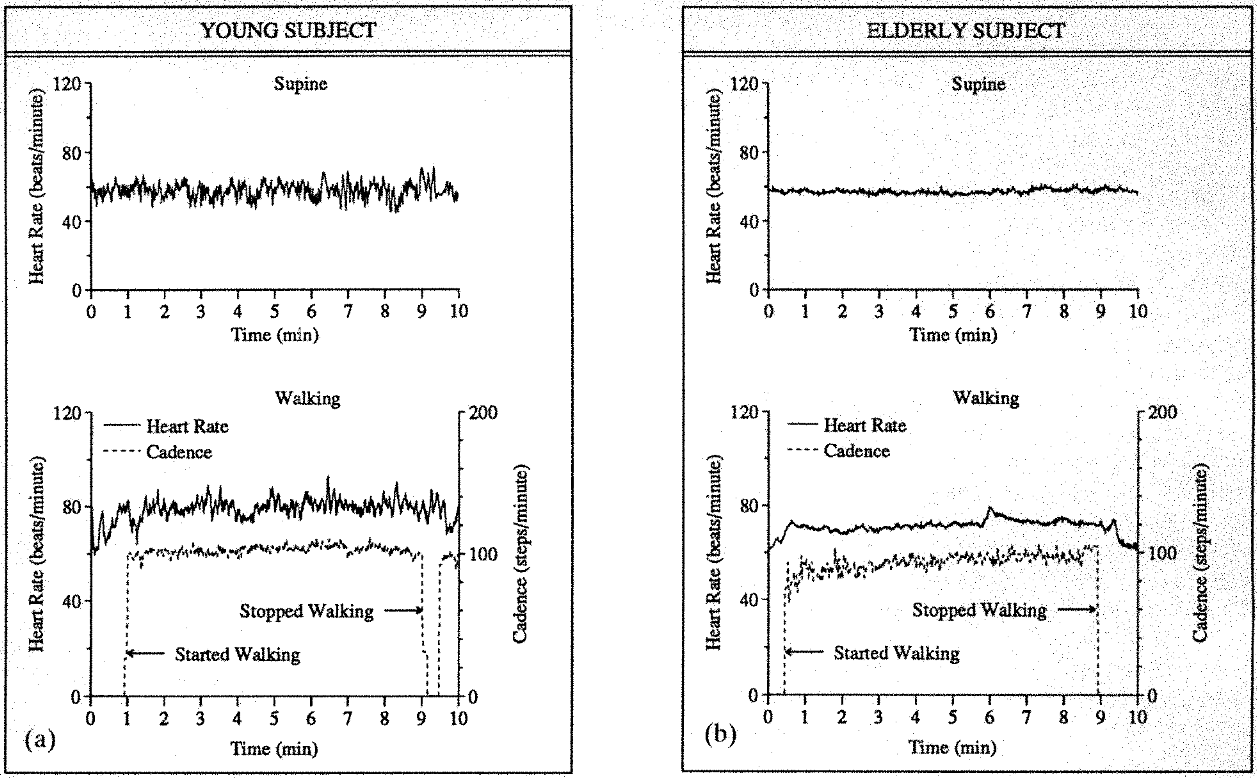


FIGURE 3. Heart rate and cadence time series for young *(a)* and elderly *(b)* subjects.

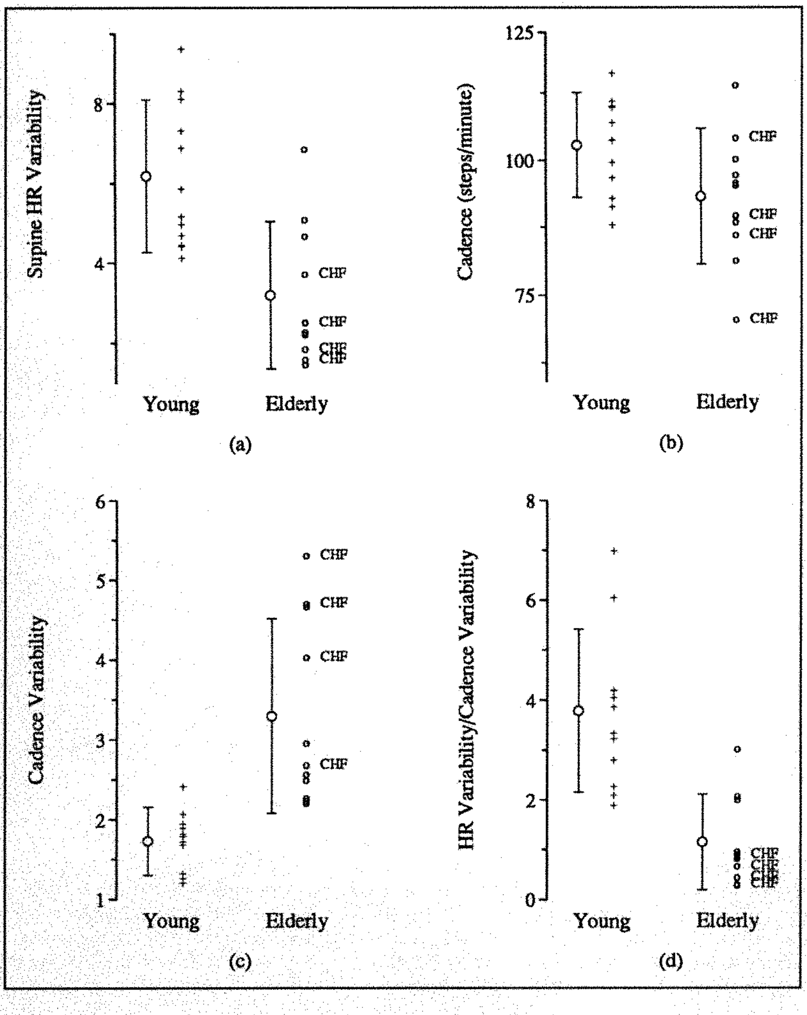


FIGURE 4. Variability of heart rate (HR) and cadence in young and elderly subjects. *(a)* HR variability in young and elderly subjects during supine rest (young 6.2 ± 1.8% and elderly 3.2 ± 1.7%; p <0.005). *(b)* Cadence in young and elderly subjects (young 103 ± 9 steps/min and elderly 93 ± 12 steps/min; p >0.05). *(c)* Cadence variability in young and elderly subjects (young 1.7 ± 0.4% and elderly 3.3 ± 1.2%; p <0.0001). *(d)* Ratio of supine HR to cadence variability in young and elderly subjects (young 3.8 ± 1.5 and elderly 1.2 ± 0.9; p <0.0005). *Errors bars* correspond to mean ± SD. *Plus signs* denote young adults; *circles* denote elderly adults with no history of congestive heart failure or coronary artery disease; *circles and CHF* denote elderly adults with history of congestive heart failure.

acute illness, sinus rhythm during supine rest, stable medications and the ability to ambulate independently. All subjects provided informed consent and medical histories. Mean age of the young subjects (2 women and 10 men) was 27 ± 5 years, and that of the elderly ones (7 women and 4 men) was 76 ± 5 years. Four elderly subjects had history of congestive heart failure (New York Heart Association functional class I or II); 2 also had history of coronary artery disease. Two elderly subjects were receiving calcium antagonists and 2 were receiving β blockers. Young subjects were not receiving any medications and had no history of any cardiovascular or gait-related disorder.

Experimental protocol: Subjects refrained from eating for ≥ 1 hour before the study, and testing was performed ≥ 2 hours after intake of medications. Subjects rested in the supine position for 21 minutes, stood in place for 6 minutes, and then walked for 8 minutes. Subjects were instructed to walk continuously at a normal, comfortable pace. All subjects wore their own walking shoes or sneakers (high heels were not worn).

Electrocardiogram and cadence analysis: Electrocardiographic data were analyzed during the last 5 minutes of supine rest (after 16 minutes of rest) and for the 5-minute period after 2 minutes of walking. During these periods, the mean HR and the HR coefficient of variation (100 × SD/mean) were calculated for subjects with <5% of ectopic beats. We also computed the frequency spectrum of HR and cadence to examine the relation between beat-to-beat changes in HR and cadence. The spectrum was computed using conventional, autoregressive, maximal entropy estimation techniques with a 12-pole model.[9] Spectral analysis has been used similarly to examine the relation between respiration, blood pressure and HR; peaks at similar locations in the spectra reflect an interaction between instantaneous regulation of HR, respiration and blood pressure.[10-13]

The cadence coefficient of variation during 1 minute of walking was calculated every 15 seconds during 8 minutes of walking. To ensure that comparable degrees of steady state were being compared, results during the 1-minute periods with the lowest cadence coefficient of variation were used for comparisons (defined as cadence variability). Furthermore, the ratio of HR variability to cadence variability was calculated for each subject to quantify the relation between these 2 indexes of variability and to obtain an overall measure of variability.

Results are reported as mean ± SD. The Wilcoxon rank sum test was used to test for differences between the young and elderly groups, and the Wilcoxon signed rank test was used to test for intragroup differences between the supine and walking experimental phases. These are nonparametric tests requiring no assumptions concerning the underlying distribution of the 2 groups. Statistical analysis was performed using SAS software programs (Cary, North Carolina). Statistical significance was defined as $p \leq 0.05$. Standard linear regression was also performed using SAS software.

RESULTS

A high-quality footfall signal was obtained in all 23 subjects. Typical time series of cadence and HR are shown in Figure 3. Step-to-step changes in cadence produce a time series similar to the instantaneous HR time series. Note the increase in HR at the beginning of walking in Figure 3a. The elderly subject shown had less HR variability than did the young one (especially at rest), whereas the young one had less variability of cadence during walking. Other differences between supine and walking states, and the interaction between the ECG and cadence are summarized in the following 3 sections.

Electrocardiographic changes during walking: In the supine position, young and elderly subjects had a similar mean HR (young 66 ± 9 beats/min, and elderly 72 ± 13 beats/min; $p > 0.05$). Rhythm was predominately sinus (>95% of beats) for all young and elderly subjects, and there was no sustained ectopy. During walking, HR increased significantly in both groups (young 22 ± 6 beats/min [$p < 0.002$]; and elderly 19 ± 7 beats/min [$p < 0.002$]), such that walking HR for the 2 groups was similar (young 89 ± 7 beats/min; and elderly 90 ± 13 beats/min [$p > 0.05$]). Because the quality of the electrocardiographic recording was inadequate for 2 young and 1 elderly subject, mean HRs are reported for 10 young and 10 elderly subjects. In general, there was no significant increase in ST depression or ectopy during walking. However, in 1 elderly subject, the frequency of ectopic beats markedly increased from 4.5 to 8.0%. In a second elderly subject, the HR rhythmicity changed dramatically from supine rest to walking. In that subject, normal sinus rhythm produced a flat time series with no fluctuations during supine rest (as in Figure 3b), but during walking, a wandering atrial pacemaker rhythm produced a HR time series with pronounced variability, with fluctuations like that normally seen in the young (e.g., Figure 3a).

Young subjects had significantly more HR variability during resting (young 6.2 ± 1.8% and elderly 3.2 ± 1.7%; $p < 0.005$) and walking (young 5.0 ± 1.4% and elderly 2.3 ± 0.5%; $p < 0.005$). For both groups, there was a slight reduction in HR variability in going from supine to walking (young −1.3 ± 2.2% and elderly −0.8 ± 1.4%), but this was not statistically significant in either group. Analysis of HR coefficient of variation during walking was not performed in the elderly subject with >5% ectopic beats, in the one with wandering atrial pacemaker or in those with inadequate electrocardiographic quality. Although elderly subjects generally had less HR variability than did young adults, variability in 3 elderly ones was within the range of the young (Figure 4a).

Cadence and cadence variability: Mean cadence (steps/min) for young subjects was slightly larger than that for elderly ones (young 103 ± 9 steps/min and elderly 93 ± 12 steps/min; $p > 0.05$), but there was considerable overlap between the groups (Figure 4b). Although cadence was similar, cadence variability was significantly larger in elderly subjects (young 1.7 ± 0.4% and elderly 3.3 ± 1.2%; $p < 0.0001$) (Figure 4c). Cadence variability of elderly subjects appeared to fall into 2 groups. One group had slightly more variability than the young subjects, and the second one had more than twice that of the young. Three of 4 subjects in the group

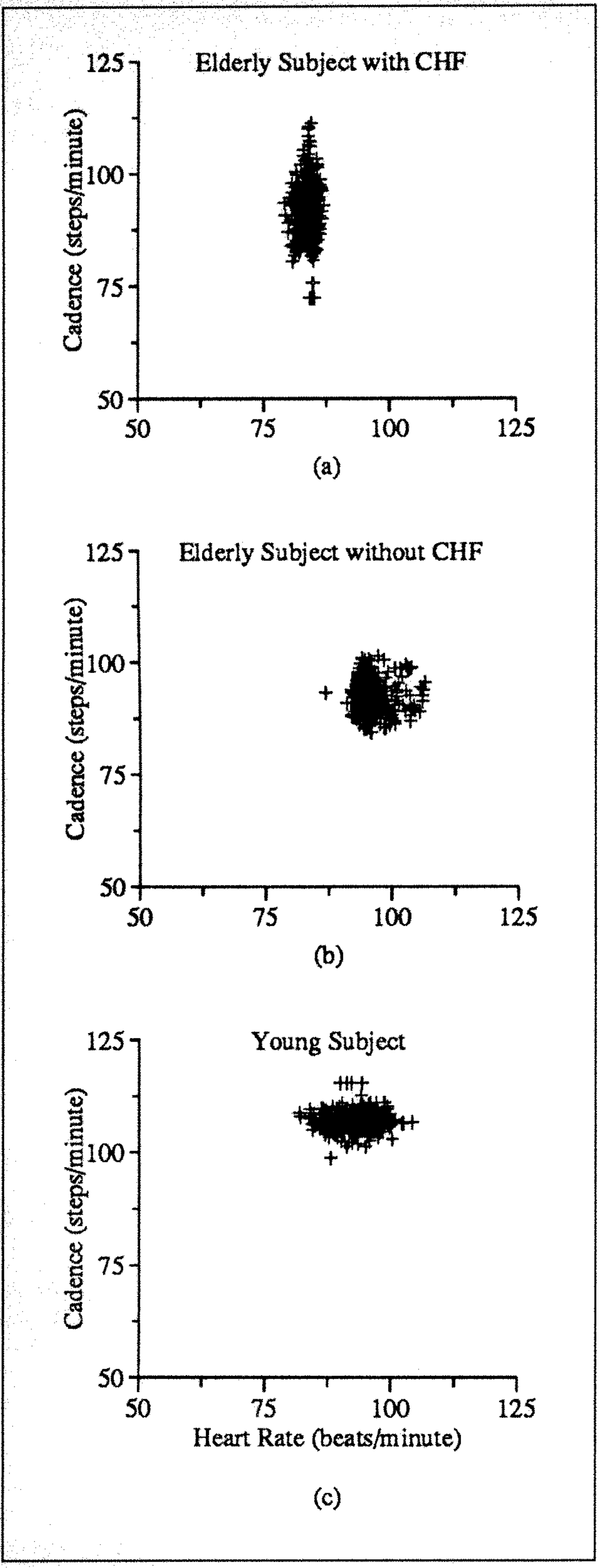


FIGURE 5. Cadence and heart rate (HR) during walking. *(a)* Elderly subject with history of coronary artery disease and congestive heart failure (CHF), *(b)* elderly subject with no history of cardiac disease, and *(c)* young subject. In subject with congestive heart failure *(a)*, there is little change in HR despite wide variations in cadence, but in healthy elderly subject *(b)* and young adult *(c)*, HR fluctuates widely, whereas there is less step rate variability.

with increased cadence variability had history of cardiac disease. In contrast, elderly subjects with greater HR variability (like young ones) also had cadence variability like the young.

Associations between heart rate and cadence: The ratio of HR variability to cadence variability was significantly larger in young subjects (Figure 4d), using both supine (young 3.8 ± 1.5 and elderly 1.2 ± 0.9; $p < 0.0005$) and walking (young 2.9 ± 1.0 and elderly 0.8 ± 0.4; $p < 0.0005$) HR variability. Elderly subjects with ratios >2 (more like the young than the other elderly) were the same 3 who had increased HR variability (Figure 4a) and reduced cadence variability (Figure 4c). In contrast, subjects with cardiac disease and several other elderly had a much lower ratio of HR to cadence variability. The differences in cadence and HR variability among the elderly are further shown in Figure 5. Some elderly subjects had no HR variability during walking (Figure 5a), whereas their cadence fluctuated widely; others (Figure 5b) had moderate amounts of HR variability and low cadence variability, as seen in the young (Figure 5c).

There were some subjects in whom the small-scale beat-to-beat and step-to-step changes in HR and cadence were clearly related. Figure 6 shows 1 example. For this elderly subject, HR and cadence were both periodic at approximately the same fundamental frequency (0.06 Hz). Results of a young subject who had similar periodicity in HR and cadence are shown in Figure 7a. Similar peaks were observed in the spectrum at approximately the same frequency (0.06 to 0.1 Hz) in other subjects; however, in some cases, the peaks occurred only in HR (Figure 7b), and in others, it occurred only in cadence (Figure 7c). Whereas there were peaks in the HR power spectrum in this frequency band (0.06 to 0.1 Hz) in all young and several elderly subjects, there was no consistent difference between young and old with regard to co-occurrence of the spectral peaks.

There was an inverse, exponential relation between HR and cadence variability across all subjects (supine HR vs cadence variability: $r = -0.73$, $p < 0.0001$; walking HR vs cadence variability: $r = -0.65$, $p < 0.005$). High HR variability was usually coupled with low cadence variability, and low HR variability was most often observed with high cadence variability (Figure 8). There was overlap between young and old subjects, but the young generally had high HR and low cadence variability. Elderly subjects (especially those with history of cardiac disease) tended to have low HR and high cadence variability. However, there were some elderly subjects with high HR and low cadence variability, like the young. Thus, even within the elderly group, the inverse relation between variability of HR and cadence persisted ($r = -0.53$).

DISCUSSION

Using a modified ambulatory monitor, we demonstrated a new means to evaluate the relation between the ECG and gait. The concurrent recording of ECG and cadence enabled assessment of interactions between ECG and walking, and proved useful in several respects.

We showed activity-related changes in HR, rhythm and HR variability that would probably be useful in determining disease/therapy characteristics, as well as idiosyncratic medication effects. In this study, we used a 2-channel Holter recorder and recorded the footfall signal on the second channel. In practice, walking cadence can be recorded on the third channel of a 3-channel Holter recorder, enabling complete 2-channel assessment and diagnosis of ischemic electrocardiographic changes, as well as footfall information. The results suggest that with only modest expense, the modified ambulatory monitor is a useful means to noninvasively assess cardiovascular and gait function.

Previous studies showed that normal aging blunts HR variability[1-4,14,15] and that HR variability is also reduced in patients with congestive heart failure,[5,16] coronary artery disease[7] and diabetes.[6] Other studies have also found associations between increased gait variability and nervous system pathology[17-19] and falling,[18,20,21] whereas the direct effect of aging on gait variability is controversial.[21-23] The present study is unique in measuring both of these parameters in the same subjects. We found an inverse relation between HR and cadence variability. In several elderly subjects, high HR variability typical of young adults was present, but in others, HR variability was severely reduced. Reduced HR variability was probably a corollary of "normal" aging in some subjects, whereas in others, this was likely due to the cumulative effects of cardiac disease and aging. All subjects with reduced HR variability also had the highest cadence variability and the lowest ratio of HR to cadence variability. This suggests that certain consequences of aging or pathology may affect both control of HR and gait.

Other observations on the interactions between HR and walking cadence imply that there may be a direct

FIGURE 6. Correlation of heart rate (HR) and cadence during steady state walking. For this subject, beat-to-beat and step-to-step changes in HR and cadence were both periodic at approximately 0.06 Hz, as seen in *(a)* and elucidated in *(b)*. Results are presented for a 71-year-old woman with no significant medical history. Time series and spectral analysis of HR during supine rest and standing also revealed similar periodicity at 0.06 Hz.

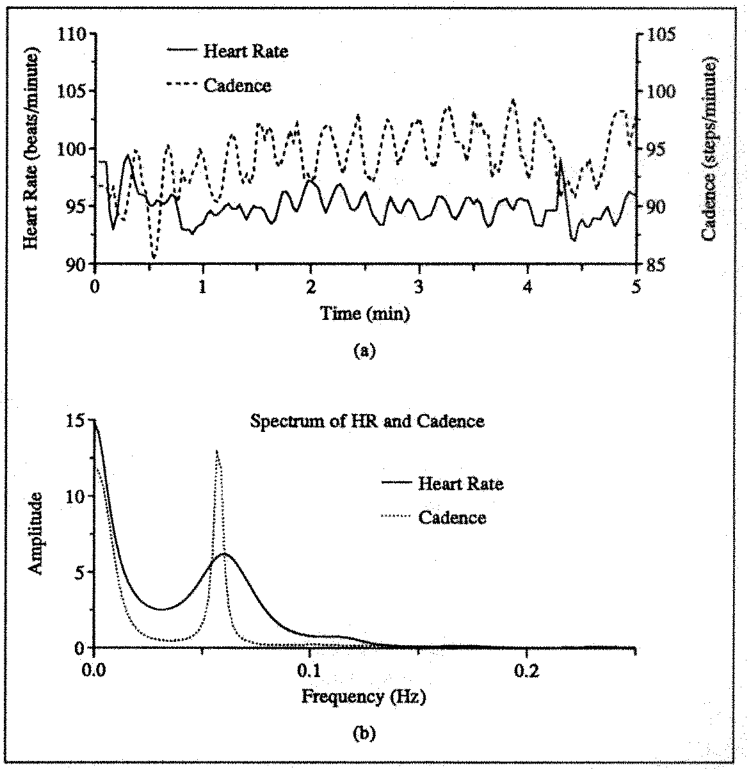
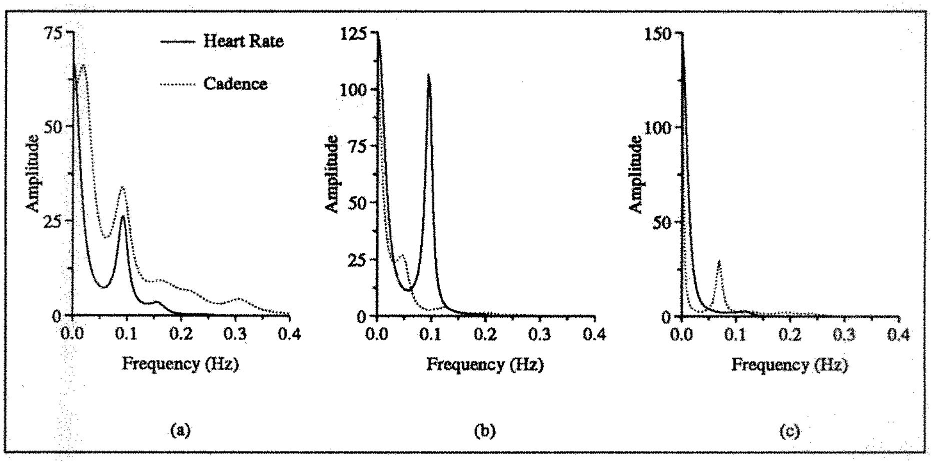


FIGURE 7. Spectral analysis of heart rate and cadence during walking. Spectrum in *(a)* and *(b)* are from young subjects, and *(c)* is from elderly one. Amplitude is presented in arbitrary units. See text for explanation.



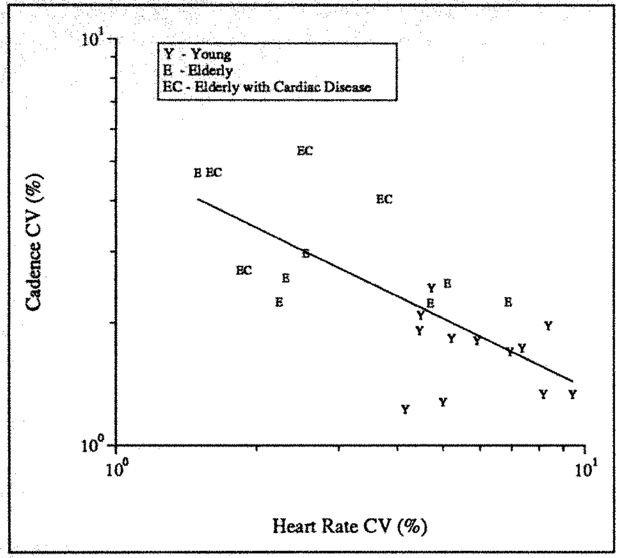


FIGURE 8. Cadence variability (CV) as function of heart rate variability. Inverse relation between cadence and supine heart rate variability was exponential with correlation coefficient of −0.73 (p <0.0001).

relation between the physiologic control mechanisms of HR and gait. In several subjects, there were significant similarities in the periodicity of the beat-to-beat changes in HR and cadence. It is unclear what caused these ≅17-second cycles in HR and cadence, and if HR and cadence were directly related or entrained by another physiologic phenomenon (e.g., respiration or blood pressure), but it is unlikely that this was due to voluntary control of walking rate. These coincident fluctuations that were also evident in HR during standing occurred at approximately the same frequency as the Mayer-like waves[7,12,13] and may therefore represent the response of the baroreceptor. In some subjects, these fluctuations occurred only in HR or cadence, but not in both. Age did not account for the differences among subjects, and both the reason for between-subject differences and the underlying cause remains unclear. However, the marked similarities of beat-to-beat changes in HR and cadence suggest interaction in the control of HR and gait, which perhaps is of neurologic origin. Although walking is primarily under voluntary control and HR is under autonomic control, some control mechanisms of HR and gait may be related.

During maximal exercise, HR variability diminishes.[24,25] Therefore, one may have expected to see a significant reduction in HR variability during walking. Although HR variability decreased, it did not reach statistical significance in either young or elderly subjects, despite the large increase in HR in both groups. This absence of significance may be a result of a type II error. However, in 3 young and 5 elderly subjects, HR variability increased slightly during walking (e.g., Figure 3a), suggesting that this absence of significance is not only a result of the number of subjects. Most likely, HR variability did not decrease significantly during walking because subjects were not exercising maximally.

Preliminary observations raise the possibility that instantaneous control of HR and gait are related. However, our findings are limited by the small number of subjects, the varying degrees of health among the elderly, our reliance on self report for patient histories, and the differences in the numbers of men and women in the young and elderly groups. Additional investigation is also necessary to further clarify the effects of aging, congestive heart failure, coronary artery disease and other pathology and medications on the inverse relation between HR and cadence variability, as well as the similarities in beat-to-beat changes in HR and cadence. Concurrent measurement of respiration and blood pressure may elucidate the cause of the similarities in beat-to-beat cadence and HR changes. Despite these limitations, there appears to be a significant dynamic interaction between the ECG and walking rate, which can best be captured by recording ECG and walking cadence simultaneously. With this ability, the modified Holter recorder should improve the assessment capabilities of Holter monitoring and enrich our understanding of cardiovascular regulation and the relation between changes in the ECG and walking.

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Impact of Food on the Pharmacokinetics and Electrocardiographic Effects of Sustained Release Verapamil in Normal Subjects

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To evaluate the impact of food on the pharmacokinetics and electrocardiographic effects of sustained release (SR) verapamil tablets, 9 healthy men each received 3 single doses of verapamil in a randomized, crossover manner: 10 mg of intravenous verapamil, 240 mg SR verapamil on an empty stomach, and 240 mg SR verapamil with a standardized meal. PR intervals and racemic verapamil serum concentrations were measured serially over 30 hours after administration. The time to peak concentration was longer (7.5 ± 3.0 vs 4.4 ± 2.3 hours), resulting in a lower peak verapamil serum concentration (118 ± 43 vs 175 ± 50 ng/ml) when SR verapamil was administered with food ($p < 0.05$). Food tended to decrease the bioavailability of SR verapamil (34 ± 12 vs 49 ± 14%), although this difference did not reach statistical significance ($p = 0.065$). Precipitous or exaggerated release of verapamil from the SR tablet was not observed in any subject during the fasting state. Prolongation of the PR interval paralleled these alterations in serum concentration. The maximal change in the PR interval was greater (21 ± 8 vs 14 ± 5%; $p < 0.05$) when SR verapamil was given in the fasting state. Although an exaggerated verapamil release or effect was not observed, food significantly altered the absorption and electrocardiographic effects of a single dose of SR verapamil. Manipulation of the administration condition may be helpful in achieving desired outcomes.

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A concern with once-daily sustained release (SR) dosage forms is the potential for a precipitous release of a relatively large amount of drug. This could cause either abrupt toxicity shortly after ingestion or loss of therapeutic effect, or both, by the end of the dosing interval. Although it is recommended to take the original SR verapamil tablet with food,[1] it is unclear if this problem exists when the tablet is given in the fasting state. The original SR tablet is designed to release verapamil in a constant fashion[1,2]; however, the consequences of coadministration with food on the cardiovascular effects have only recently been reported and further clarification is needed.[3] This study characterizes the pharmacokinetics of verapamil when administered to healthy subjects with the oral SR tablet in the fasting and nonfasting states. Furthermore, the change in PR interval was measured to evaluate the impact of administration condition on drug effect.

METHODS

Subjects and procedures: This study was approved by the University Institutional Review Board for Human Investigations and all subjects provided written informed consent before study entry. Nine healthy, nonsmoking men (aged 25 ± 3 years, weight 73.9 ± 10.1 kg) were studied. A medical history, physical examination, 12-lead electrocardiogram, serum chemistries and complete blood cell count were performed to evaluate the health of each volunteer. Subjects were asked to abstain from any alcohol, medication or caffeine use for 48 hours before the start of each study phase until its completion. The subjects participated in each of 3 phases in a randomized, open-label, crossover manner with at least a 1-week washout between each phase. The 3 phases were: (1) 10 mg of verapamil administered intravenously; (2) a single dose of SR verapamil 240 mg (Isoptin SR®, Knoll Pharmaceuticals) administered on an empty stomach; and (3) a single dose of SR verapamil 240 mg (Isoptin SR®, Knoll Pharmaceuticals) administered immediately after a standardized breakfast. All subjects fasted for 3 hours after dosing.

Each study day began after an overnight fast. An intravenous catheter flushed with a dilute heparin solution was placed in the arm of each subject for blood sampling. A Holter monitor was also placed on each subject to continuously record a lead II rhythm strip throughout the 10-hour study day. Blood pressure measurements were obtained in duplicate with an automated blood pressure device (HealthTeam model 8175, M.E. Team Inc., South Plainfield, New Jersey) to de-

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crease measurement variability. Subjects were placed in a supine position starting ≥15 minutes before intravenous verapamil and remained supine until 2 hours after administration. After a baseline blood pressure and blood sample were obtained, 10 mg of verapamil was administered through an intravenous catheter, in the arm contralateral to that of blood sampling, over 5 minutes via a volumetric syringe pump. Blood pressure and a 10 ml blood sample were obtained at 5, 10, 15, 30, 45 and 60 minutes, and at 1.5, 2, 4, 6, 8, 10 and 24 hours after infusion. The event marker of the Holter monitor was depressed at the time of blood sampling. Blood samples were allowed to clot at room temperature, then centrifuged and separated. The serum was stored at −70°C until the time of analysis. These procedures were repeated for each of the 2 oral verapamil phases, except that the patients were studied in a sitting position after 15 minutes of rest. Blood pressure measurements and a 10 ml blood sample were obtained at 1, 2, 3, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 12, 24 and 30 hours after drug administration.

Racemic verapamil serum concentrations were measured by reverse-phase, high-performance liquid chromatography using fluorescence detection. Serum samples were spiked with the internal standard (metoprolol) and extracted by the liquid-liquid method of Harapat and Kates.[4] Separation and quantitation of verapamil and norverapamil were performed by the method of Kuwada et al,[5] with the substitution of octane-sulfonic acid for heptane-sulfonic acid in the mobile phase. The intra- and interday coefficients of variation were <11% for verapamil and <7% for norverapamil. The lower limit of detection for verapamil was 1 ng/ml.

Pharmacokinetic analysis: The peak verapamil serum concentration and time to peak concentration were determined graphically from the individual concentration-time curves. Linear regression of the terminal slope of the concentration-time curve was used to determine the terminal rate constant. The apparent elimination half-life was calculated from the terminal rate constant. The area under the concentration-time curve (AUC) was calculated using the trapezoidal rule and extrapolated to infinity. The absolute bioavailability of oral racemic verapamil under each administration condition was calculated by the equation: $F = [AUC(oral) \times dose(intravenous)]/[AUC(intravenous) \times dose(oral)]$. The area under the moment curve was calculated for the intravenous dose using the trapezoidal rule extrapolated to infinity in order to calculate the volume of distribution and clearance using standard noncompartmental equations for a constant rate infusion of short duration.[6]

Electrocardiographic and hemodynamic analysis: Electrocardiographic rhythm strips at the time of blood sampling were printed from the Holter monitor recording. Heart rate and PR intervals were determined from the mean of 10 consecutive cardiac cycles on each rhythm strip. Measurements were obtained by a single investigator unaware of the patient's treatment assignment. Heart rate, PR interval, and systolic, diastolic and mean arterial blood pressures were statistically evaluated over time within treatment phases to detect significant changes from baseline, as well as to determine the duration of pharmacologic effect. Percent changes from baseline were calculated for PR interval to compare the maximal effect and time to maximal effect between treatment phases.

Statistical analysis: A nonparametric analysis was performed since the data were not normally distributed according to the Shapiro-Wilk test. The effect data were ranked within each phase, and an analysis of variance for repeated measures was performed on the ranked data to evaluate PR interval, heart rate and blood pressures over time. The Student-Newman-Keuls multiple comparison test was performed to determine which time points differed from baseline. The pharmacokinetic and electrocardiographic parameters of the 2 oral verapamil phases were compared using the Wilcoxon signed rank test.[7] A p value <0.05 was considered significant for all comparisons. All data are reported as mean ± standard deviation unless otherwise noted.

RESULTS

Pharmacokinetics: The rate and extent of oral absorption of verapamil from the SR tablet were quite variable regardless of administration condition. However, a precipitous release of verapamil from the SR tablet was not observed with either administration condition. Figure 1 demonstrates the spectrum of absorption profiles observed. More than 1 modal concentration was observed in 5 subjects. When this occurred, the largest modal concentration was selected as the peak concentration. The pharmacokinetic parameters for the intravenous reference dose and the 2 oral doses of verapamil are listed in Table I. Coadministration with food significantly reduced the rate of absorption of verapamil from the oral SR tablet, resulting in a prolongation in the time to peak concentration (7.5 ± 3.0 vs 4.4 ± 2.3 hours; $p < 0.05$) and a reduction in the maximal observed verapamil concentration (118 ± 43 vs 175 ± 50 ng/ml; $p < 0.05$) (Figure 2 and Table I). Although administration with food tended to reduce the bioavailability of verapamil from the SR tablet, this decrease was not statistically significant. There were also no significant differences between the apparent elimination half-lives after oral administration with or without food; however, the apparent elimination half-life of verapamil after each oral dose was greater than that after intravenous administration. The verapamil/norverapamil ratio of the AUC for the fed and fasting states were similar since the norverapamil concentrations mirrored those of verapamil over time.

Electrocardiographic and hemodynamic effects: No significant changes in mean blood pressures or mean heart rate were observed over time. The magnitude and time course of PR interval prolongation between persons were quite variable. Significant prolongation of PR interval from baseline was observed in both the fed and fasting phases (Figure 2). However, significant prolongation was observed at only 2 time points after administration with food, whereas significant prolongation was evident for a 5.5-hour time period after administration on an empty stomach. Additionally, oral administration during a fasting state resulted in a greater maximal pro-

TABLE I Pharmacokinetic and Electrocardiographic Parameters

Parameter	Verapamil (10 mg intravenous)	Verapamil SR Oral Administration Fasting	Verapamil SR Oral Administration with Meal	p Value
Vss (liters/kg)	3.03 ± 0.63			
CL (liters/hour/kg)	0.919 ± 0.161			
Cmax (ng/ml)		175 ± 50	118 ± 43	$p < 0.05$
Tmax (hours)		4.4 ± 2.3	7.5 ± 3.0	$p < 0.05$
Bioavailability (%)		49 ± 14	34 ± 12	$p = 0.065$
Half-life (hours)	2.9 ± 0.39	7.6 ± 1.1	6.6 ± 2.8	
AUC ratio (verapamil/ norverapamil)		0.82 ± 0.10	0.82 ± 0.17	
Max % PR		21 ± 8	14 ± 5	$p < 0.05$
Tmax % PR (hours)		5.5 ± 2.1	6.2 ± 2.2	

Data are expressed as mean ± standard deviation. Parameters from the 2 oral doses were statistically compared with significance noted under p value. AUC ratio (verapamil/norverapamil) = ratio of the areas under the concentration-time curves of verapamil and norverapamil; CL = clearance; Cmax = peak serum concentration; Max % PR = maximal percent prolongation of PR interval; SR = sustained release; Tmax = time of peak serum concentration; Tmax % PR = time of maximal prolongation of PR interval; Vss = volume of distribution at steady state.

longation of the PR interval (21 ± 8 vs 14 ± 5%; $p < 0.05$), although the time at which maximal prolongation occurred did not differ significantly (Table I). Oral administration of verapamil produced a headache in 6 of 9 subjects. This did not appear to be related to the administration condition since 3 subjects experienced a headache during the fasting phase and 3 subjects during the fed phase.

DISCUSSION

Previous experience with SR dosage forms has shown that food can have a significant impact on drug release and absorption.[8] Administration of a SR theophylline preparation with food resulted in a precipitous release of theophylline, yielding a 57% increase in drug absorption, a 118% increase in peak serum concentrations, and signs of toxicity in 4 of 8 subjects. To alleviate similar concerns regarding administration of the SR verapamil tablet in the fasting state, this study was undertaken to evaluate the impact of the administration condition on the disposition of verapamil, and the resulting cardiovascular effects.

Pharmacokinetics: The pharmacokinetic parameters of verapamil after intravenous administration were similar to those previously reported for healthy subjects.[9-12] There was considerable interindividual variability in the rate, pattern and extent of absorption of verapamil from the SR tablet when given in both the fed and fasting states. However, alterations in absorption and resulting drug effect were not as dramatic as those reported for a SR theophylline product.[8] Administration during a fasting state did result in faster absorption, accompanied by a 48% increase in peak concentration. This increase in peak concentration is consistent with previous reports of a 53 and 46% increase in peak concentration after the administration of the immediate release and SR dosage

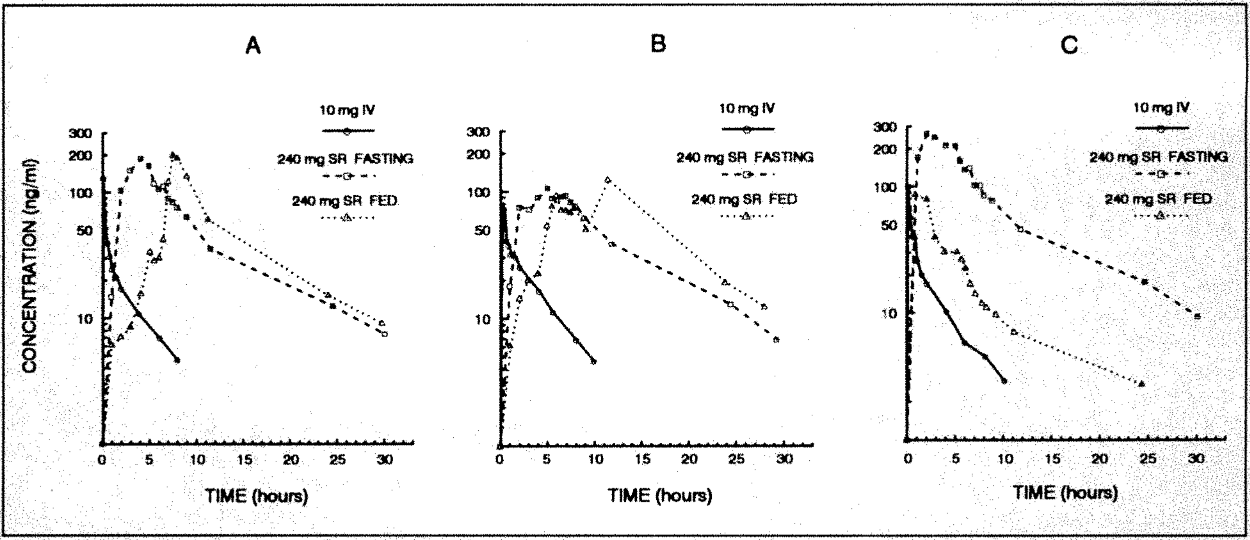

FIGURE 1. Verapamil serum concentrations versus time after intravenous (IV) dosing, oral dosing in the fasting state and oral dosing in the fed state for each of 3 individual study subjects. *A*, peak concentrations are similar with faster absorption in the fasting state; *B*, 2 modal concentrations are observed after administration with food with a higher peak concentration than the fasting state; *C*, administration with food resulted in faster absorption and a lower peak concentration. SR = sustained release.

form, respectively, in the fasting state.[3,13] In both of these reports,[3,13] as well as in this study, a significant reduction in the time to peak concentration was observed in the fasting state. This observation may be explained by delayed gastric emptying or alterations in the interactions of intestinal fluids with the tablet surface after coadministration with food,[2] which would result in slower absorption and lower peak concentrations. A reduction in bioavailability could also explain decreased peak concentrations. Although a trend toward reduced bioavailability was observed after administration with food, this 30% decrease was not statistically significant. A similar observation has been implied in a previous review.[14] The relative delivery of verapamil and norverapamil after administration in the fed and fasting state was similar: norverapamil concentration-time curves mirrored those of verapamil and the ratio of the respective AUCs did not differ. This suggests that the administration condition does not alter first-pass metabolism. Also, the apparent half-lives after the 2 oral phases of the study did not differ from each other, suggesting that there is no alteration in the rate of elimination.

Electrocardiographic effects: There was considerable variability in prolongation of the PR interval with respect to both magnitude and time course. This is not surprising considering the variability in the verapamil concentrations after administration of the SR tablet, and the demonstrated relation between PR interval prolongation and racemic verapamil serum concentrations.[9-11,15,16] Administration of the SR verapamil tablet in the fasting state produced a greater maximal prolongation of PR interval, which paralleled the higher peak serum concentrations. Additionally, significant PR interval prolongation was maintained from 2 to 7.5 hours after administration in the fasting state. In comparison, significant PR prolongation was observed at only 7 and 8 hours after administration with food. Therefore, the greater effect seen earlier in the fasting state did not appear to result in a premature loss of effect. Rather, higher peak serum concentrations were obtained in the fasting state, resulting in a greater prolongation of PR interval, the decline of which paralleled the decline in serum concentrations.

Translating the alterations of pharmacologic effect from controlled, single dose studies to the alterations of clinical effect with chronic administration is difficult. In addition to the expected drug accumulation on chronic dosing to steady-state, the clearance of verapamil appears to decrease with continued administration.[17] One would therefore expect larger or more sustained effects with chronic dosing. Indeed, sustained blood pressure reductions with once-daily administration of SR verapamil have been shown.[18,19] However, the duration of action on the atrioventricular node lasted no >8 hours after a single dose in either the fasted or fed state. Based on this observation, one could question the wisdom of administering SR verapamil on a once-daily basis for the treatment of supraventricular arrhythmias. Evidence supporting once-daily administration of SR verapamil for the treatment of supraventricular arrhythmias is scarce.[20] The clinical relevance of the short duration of atrioventricular node effects may be minimized with chronic dosing; however, the potential for greater effects on atrioventricular node conduction should be considered when SR verapamil is given in the fasting state because higher peak concentrations may be consistently achieved.

Although greater peak serum concentrations were observed in the fasting state, concerns regarding precipitous or exaggerated absorption of verapamil from the SR tablet when taken on an empty stomach appear unfounded. Administration in the fasting state significantly increased the rate of absorption and the effect on atrioventricular node conduction as measured by prolongation of the PR interval. This echoes the higher peak concentrations observed. Anticipating this food ef-

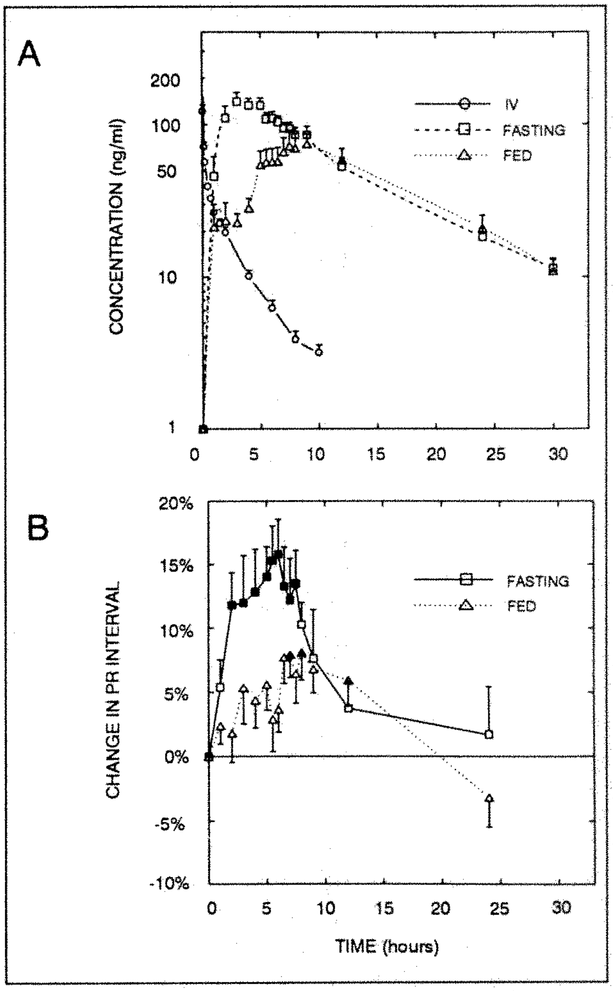

FIGURE 2. ***A,*** **verapamil serum concentrations versus time after a 10 mg intravenous dose, a 240 mg oral sustained release (SR) dose in the fasting state and a 240 mg oral SR dose in the fed state. Data presented are the mean values of the 9 healthy subjects during each of the 3 treatment phases.** ***Error bars*** **represent standard error of the mean.** ***B,*** **change in PR interval versus time after the administration of a 240 mg oral verapamil SR dose in the fasting state and in the fed state. Data presented are mean values of the 9 healthy subjects during each of the 2 treatment phases.** ***Error bars*** **represent standard error of the mean.** ***Solid markers*** **represent values that statistically differ from baseline.**

fect is of practical concern because manipulation of the administration condition may be helpful in achieving desired outcomes.

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Differences in Men and Women in Coronary Artery Disease, Systemic Hypertension and Their Treatment

Mary Ellen Kitler, PhD, FCP

On average, women outlive men by 7.5 years. Women who have lived to age 65 years will likely live another 18 years, whereas comparable men will live only another 14. Therefore, women are disproportionally represented among older age groups,[1] and it has been said that the aging of the population equals a "feminizing" of the elderly.[2]

The interaction of older women with the health care system has been well-established. In 1984, women constituted 60% of the Medicare elderly population, and in 1986, they constituted 71% of the population entitled to both Medicaid and Medicare benefits.[3] Older women are less likely to have private health insurance, and they have fewer personal financial resources for health care than do older men.[4] In 1985, women accounted for 558 drug mentions* per 100 population compared with 383 for men. Although women constitute 51% of the population, they account for approximately 60% of all prescription drug mentions. This has been ascribed to the fact that women have a longer life expectancy. Older people, it is thought, receive more drugs than do younger ones. Furthermore, any group of women will be much more heterogeneous than any age-matched group of men. Some factors that may contribute to these differences are the "empty nest" syndrome, the confounding effects of premenopausal and menopausal changes, the potential social and psychological problems of being a widow (there are more widows than widowers), and potentially different health beliefs and behaviors.[5,6] Also important are the different presentations, approaches to and outcomes of different diseases, including coronary heart disease, in the 2 genders.

CORONARY ARTERY DISEASE

Since 1950, the incidence of coronary artery disease has increased in women while it has decreased in men.[7] Coronary heart disease has been a leading cause of morbidity and mortality in women since the early 1900s, accounting for the death of 52% of women in the United States compared with 46% of men. It is estimated that approximately one half million women die from coronary artery disease each year. The disease is the leading cause of disability in women in the U.S. and accounts for well over one third of all hospital stays of women aged >55 years.[8] Almost one third of first-listed diagnoses among hospital discharges for persons aged ≥65 years were diseases of the circulatory system. The leading cause of death among older people in 1984 was heart disease (2,186/1,000,000 people aged ≥65 years, increasing to >7,251/100,000 for those aged ≥85 years). Although the elderly constitute only 13% of the U.S. population, 80% of all deaths due to acute myocardial infarction occur in those aged >65 years. Of these deaths, 60% occur in patients aged ≥75 years, a group in which women outnumber men by a ratio of 2:1. After coronary artery disease is manifest, the case fatality rate for women exceeds that for men. After myocardial infarction, women (and in particular black women) appear to be at increased risk for reinfarction and death, although some of this risk may be ascribed to advanced age and severity of the disease.[9,10] Furthermore, whereas 1 in 5 men has had a coronary event by age 60 years compared with only 1 in 17 women, women are more likely to die of a first heart attack.[11] However, various studies have shown that women with coronary artery disease are treated quite differently from men.

Women may be referred for coronary angiography much less often[12] and to coronary artery bypass surgery at a much more advanced age and with greater severity of illness,[13] and when hospitalized for coronary heart disease, undergo fewer major diagnostic and therapeutic procedures[14] than men. Therefore, physicians pursue less aggressive diagnostic and management approaches to coronary disease in women than in men, despite the greater cardiac disability in women.[15]

Why the disparity? It was believed that many noninvasive tests for coronary artery disease are less accurate in women than in men[16] and that the predictive value of a stress test is lower in women than in men, although that conclusion has been questioned.[17] Women are also more likely to present with uncomplicated angina as the chief symptom,[18] leading to the belief that heart disease is better tolerated by women than by men and that angina is less likely to be followed by serious cardiovascular events in women than in men.[19] Women who present with a heart attack tend to be older and sicker than men, and to have hypertension and diabetes, but are less likely to have had a previous myocardial infarction. After women present with a heart attack, they are more likely to have complications (including congestive heart failure and supraventricular arrhythmias) and to be more susceptible to stroke, myocardial rupture and major infarct extension. Clearly, treatment of women (and in particular, older women) should be based on poten-

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*Drug mentions represent drugs prescribed, recommended or administered in any medical setting by a private physician who has an office-based practice. Mentions reflect usage, but should not be interpreted as being equivalent to patients or prescriptions.

tial benefit[20] and should not be less in quality and quantity than that offered men, including treatment for 1 of the major risk factors for coronary disease (i.e., hypertension).

HYPERTENSION

Hypertension and heart disease are 2 of the potentially modifiable risk factors that predispose subjects to stroke, the third most prevalent cause of death in the Western world. Up to 25% of acute stroke victims die within a few weeks of the event, and stroke is the major crippling disease in developed countries. Hypertension is also a major risk factor for congestive heart failure. There are approximately 250,000 to 400,000 new cases each year in the United States. Over the past 3 decades, there has been a marked reduction in death rates for heart disease, and control of hypertension is probably the major contributing factor to this decrease. Approximately half of the strokes in hypertensive patients between the ages of 65 and 79 years could have been prevented by antihypertensive treatment,[21] and death from ischemic heart disease can be reduced by >10% by antihypertensive treatment.[22]

Hypertension is a more important risk factor for heart disease in women than in men. Hypertensive women are approximately 4 times more likely to have heart disease than normotensive ones. Men's risk of heart disease increases threefold if they have hypertension.

Arterial pressure increases throughout life in Western populations, reaching hypertensive levels in almost 50% of people aged >65 years. When comparing younger and older people, the likelihood of hypertension is 57% greater for the older age group. The increase in arterial pressure was at one time thought to be beneficial at least to certain subpopulations,[23] but is now associated with an unacceptably high risk for morbidity and mortality.[24] Hypertension is the most common reason for office visits[25] and the most common indication for prescription drug use in the United States.[26]

Systolic pressure increases with age, whereas diastolic pressure increases to age 70 years and then decreases. Mean systolic pressure in men is significantly higher than in women, but diastolic pressures apparently do not differ.[27] The prevalence of increased, isolated systolic pressure may range from 10% in men aged 60 years to 37% in women aged 70 years. The prevalence of increased diastolic pressure ranges from 43% in men aged 60 years to 38% in women aged 70 years.[28] Results from the HANES II study indicate that at >65 years of age, prevalence increases to approximately 50%. There is a female and black predominance, with a prevalence as low as 35% in white men and increasing to 59% in black women.[29] Hypertension is more prevalent in African Americans aged 65 to 74 years (60%) than in whites (44%), and in black women than in black men.[30]

In the Framingham Study, hypertension was defined as blood pressure ≥160/95 mm Hg. If that classification is used, 30% of men between the ages of 65 and 74 years would be classified as hypertensive.[31] Using a blood pressure level of 140/90 mm Hg to define hypertension, 64 to 68% of the elderly would be classified as hypertensive.[32] With increasing age, the apparent gender difference between white men and women disappears, but the prevalence of hypertension in black women remains greater than in black men.[33] There is a steady increase of new hypertension within each 10-year age interval, with blacks having at least twice the incidence of whites.[33]

Treatment of all hypertensive subjects has been recommended. Early detection and treatment will result in some decrement of stroke and other cardiovascular disease risks. Management of hypertension with drugs would be the same across all age groups, but there are some population trends that suggest that particular care should be taken when treating hypertension in the elderly, perhaps women and also blacks. It is suggested that one always begin with nonpharmacologic approaches, including calcium supplementation that appears to be helpful in women.[34]

A series of randomized, controlled studies found treatment of mild hypertension effective when increased diastolic pressure was treated mainly with diuretics and β blockers.[21,35-39] Isolated systolic hypertension (affecting as many as 18% of people aged ≥80 years) is an independent risk factor for cardiovascular disease and death.[40] Its treatment with a diuretic as the first drug reduces fatal and nonfatal cardiovascular events, even in patients aged ≥80 years. Confirmation of these findings is desirable, because only 1% of all subjects screened were enrolled in this study of isolated systolic hypertension, and those enrolled were free of major cardiovascular, renal or neoplastic disorders.[41]

There is little information on treating high blood pressure in women. The National Heart, Lung, and Blood Institute is attempting to establish guidelines for treating high blood pressure in women, which would replace the standards established in 1988. Much of this "struggle" is based on a recent review of 7 major hypertension studies.[21,37,42-46] Of these studies, 3 did not include women,[42-44] 1 studied only elderly patients,[21] and 3 are thought to have been too short in duration to follow a sufficient number of women.

Elderly hypertensive patients are less often treated than are younger adults,[47] and because women are overrepresented among the elderly, they are treated less often. However, the attributable risk percentage for cardiovascular complications of hypertension is higher for women than for men.[30,48] "A striking and statistically significant difference between men and women is found when Medical Research Council (MRC) data are analyzed by gender"[46] (women constituted 48% of this MRC study). Subgroup analysis of Hypertension Detection and Follow-up Program data[37] showed that white women may be harmed by antihypertensive treatment (women constituted 46% of the study).[30] In the latter analysis, an excess mortality was demonstrated for white women treated with stepped care.[49,50]

Antihypertensive medications do not appear to be as effective in women as in men, and there is no information on their effects on serum lipids in women.[30] Treatment may be dangerous if dosages are not adjusted, because coronary arteries of women are generally narrower than those of men.[14] These arteries are likely to go into spasms when β blockers or calcium antagonists are not adjusted to the female patient. However, hazard differences may be more in favor of women than men in certain cases. For example, the relative hazard of men versus women for cardiovascular death was 1.881 on intention-to-treat analysis and ≥2.333 on randomized treatment.[51] Similar data have been presented,[52] which indicate relative hazards (men vs women) of 2.23 for cardiovascular death, 2.41 for coronary artery disease and 1.49 for stroke. However, no data have been presented that elucidated or rejected differences in treatment approaches of cardiovascular diseases, and whether white women with hypertension merit different treatment than men.

SUMMARY

Various studies have shown that women with coronary artery diseases are treated quite differently from men, although the reasons for these differences are not easily discernible and may be based on misconceptions. Furthermore, although the attributable risk percentage for cardiovascular complications of hypertension is higher in women than in men, little information on treating hypertension in women is available. There is cause for concern owing to some findings that white women may be harmed by antihypertensive treatment unless that treatment differs from that of men. Consensus on the importance of this finding has not been reached.

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Left Ventricular Shape Abnormalities in Inferior Wall Myocardial Infarction

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Many unanswered questions remain concerning the physiopathology of inferior wall myocardial infarction. Expansion and thinning of the involved area (frequently observed in the anterior infarct) are seldom demonstrated in the inferior infarct.[1-3] According to some observations, wall expansion appears related more to the site rather than to the size of the pathologic lesion.[4] Furthermore, wall motion abnormalities are usually less severe in the inferior than anterior infarct,[3,5] even when the extent of myocardial damage and the depression of global left ventricular (LV) function are equivalent.[6] In explaining the higher frequency of wall expansion in the anterior infarct, an important role has been attributed to the involvement of the anteroapical region that mainly contributes to the stretching and thinning of the necrotic area.[7] The aim of this study was to analyze LV shape abnormalities in the inferior infarct by quantitative methods and to relate them to the extent of wall motion alterations and to the severity of LV dysfunction.

LV angiograms of 61 patients (57 men and 4 women, aged 36 to 72 years, mean 57) with a prior inferior wall myocardial infarction were retrospectively selected for analysis and compared with the angiograms of 16 normal subjects (10 men and 6 women, aged 41 to 63 years old, mean 53) suspected of having heart disease who underwent diagnostic cardiac catheterization and were found to have normal cardiac anatomy, coronary arteries and LV function. Study patients had a healed inferior myocardial infarction that had occurred 3 to 11 months before the angiographic examination. No patient had thrombolytic therapy during the acute phase. All patients had a typical electrocardiographic picture of inferior myocardial infarction (Minnesota code) and demonstrated a persistent perfusion defect in the inferior territories by thallium scintigraphy. Patients with the perfusion defect located only in the lateral wall or with associated defects in the anterior territories who had undergone myocardial revascularization were not included in the study.

Catheterization was performed after withdrawal of cardiac drugs for 24 hours. LV angiography was performed in the 30° right anterior oblique projection with a power injection of 0.7 ml/kg of contrast medium at a rate of 13 to 15 ml/s. Films were obtained in mild inspiration at a rate of 50 frames/s using a 9-inch image intensifier. In each patient, 2 grids of radiopaque markers, anterior and posterior to the patient's thorax, were filmed before angiography to correct for magnification and distortion.[8] *The end-systolic frame was chosen as the smallest LV volume; the frame before mitral valve closure was chosen as the end-diastolic frame. Endocardial outlines at end-diastole and end-systole were carefully traced and digitized with 0.1 mm uniform steps (MYPAD-A3 digitizer, model K-510 mk2). Papillary muscles were included within the cavity. LV volumes were calculated by single-plane Chapman's method.*[9] *Regional wall motion was evaluated using the digitized outlines by applying the centerline method.*[10] *The systolic shortening of 90 chords, from the aortic to mitral corner, was calculated. The shortening fraction of each chord was divided by the end-diastolic perimeter of the left ventricle to avoid differences due to size. Patients with inferior myocardial infarction were compared with normal patients by calculating the Z value for each chord as follows:* $Z = (SF - Mn)/SDn$, *where SF is the measured shortening fraction, Mn is the mean, and SDn is the standard deviation of the normal values. Thus, Z is expressed as SD from the normal mean.*

The extension of LV asynergy (A%) was evaluated by calculating the percentage of the LV perimeter showing a decrease of systolic shortening ≥2 SD from the normal mean value.[11]

The reciprocal of the radius of the circle that best fits a segment of the arc centered at any specific point was calculated using a windowed Fourier series approximation of contours, in which the number of harmonics and the filter-window were locally chosen to minimize the reconstruction errors and maximize the smoothness of the curve.[12]

Curvature analysis began from the anterior aortic plane (point 1) and proceeded clockwise in 90 equidistant steps to the mitral plane (point 90). The results obtained in patients with inferior myocardial infarction were compared with those in normal subjects by calculating the Z value (coefficient of variation in SD from normal mean) of each point. Analysis programs were written in Pascal language for computers of the 80386 series and tested on a series of ventricle-shaped contours.[12] *The overall reliability of the methods (from digitizing the outline to the final output) was found to be good (r = 0.92; mean error 10% with respect to analytical values).*[12] *The analysis program enabled measurement of the length of angiographic contours from the aortic corner (point 1) to the apex (anterior hemiperimeter length) and from the apex to the mitral fornix (point 90) (posterior hemiperimeter length). The apex was defined as the point with the greatest curvature.*

We performed the Fourier shape analysis according to the method adopted by Kass et al[13] *to reconstruct the mean ventricular contour, transforming the digitized coordinates into polar form. The first 12 harmonic components of the spectrum were used. Each term was normalized for the zero-order term to eliminate the contribution*

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TABLE I Hemodynamic Data

	EDVI (ml/m^2)	ESVI (ml/m^2)	LVEF (%)
Control group (n = 16)	78 ± 16	26 ± 10	67 ± 8
Inferior myocardial infarction (n = 61)	87 ± 18	39 ± 15	56 ± 10
t test p value	NS	0.0001	0.01

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LVEF = left ventricular ejection fraction; NS = not significant.

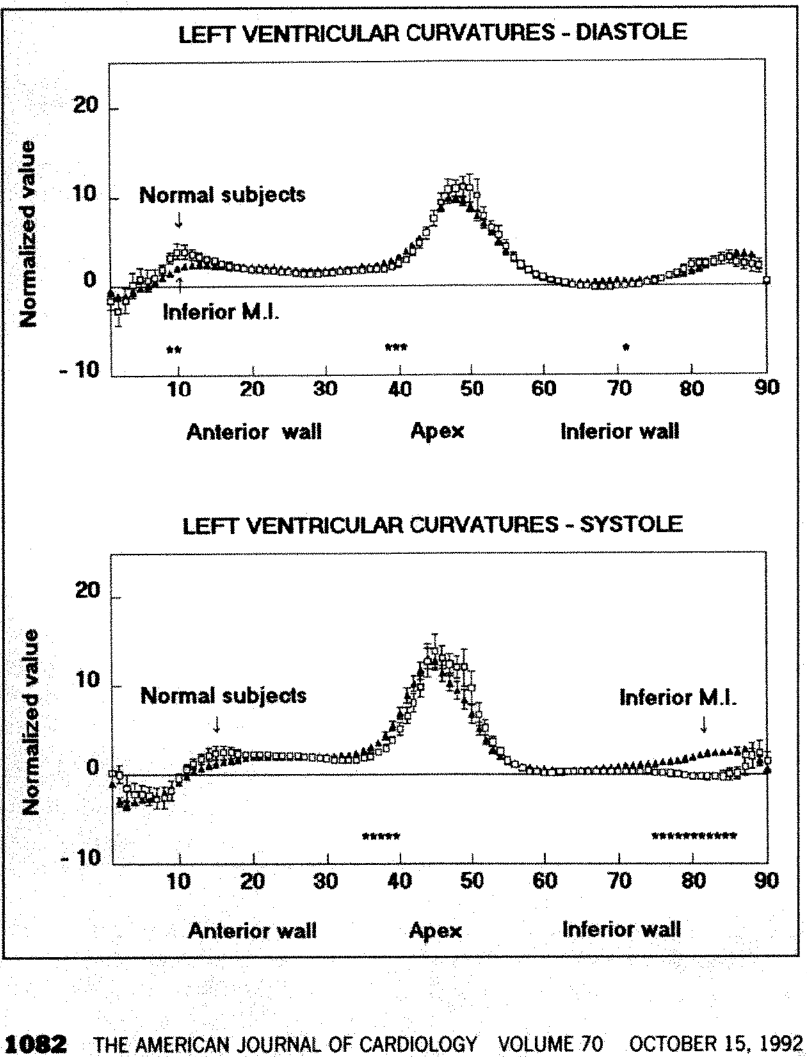
of ventricular size. The average spectrum of each group was used to reconstruct a representative mean LV contour.

Results are expressed as mean ± SD. Differences were tested with paired or unpaired t *test. Correlation coefficients between the curvature values and hemodynamic parameters were calculated. A relation was considered to be noncasual when ≥5 consecutive points showed curvature values significantly correlated with the hemodynamic parameter.*

Hemodynamic data of patients with an inferior myocardial infarct and of normal subjects are listed in Table I. End-systolic volume index significantly increased and LV ejection fraction significantly decreased in patients. Wall motion analysis (performed by the centerline method) showed a significant hypokinesia of the inferior LV wall in patients (chords 43 to 48, 61 to 82, and 89 to 90). The extent of LV asynergy (A% = percentage of LV outline with shortening fraction 2 SD below normal) was 19.4 ± 18.3. A significant inverse correlation was found between A% and LV ejection fraction ($R = -0.76$; $p < 0.001$).

The curvature values of diastolic and systolic outlines in normal subjects and patients with an inferior myocardial infarction are reported in Figure 1. Representative mean silhouettes of LV angiograms of both groups are shown in Figure 2. Analysis of regional curvature showed few significant differences between the 2 groups. In diastole, patients showed a lesser curvature at 2 points located in the anterobasal region (9 and 10) and a greater curvature at 4 points in the anteroapical (38 to 41) and 1 in the posterobasal (71) region. In systole, patients showed a significantly greater curvature at 6 points of the anteroapical (34 to 39) and 13 of the inferobasal region (74 to 86) regions. The curvature of the latter region had positive values, indicating a concavity of endocardial contour toward the LV cavity. In normal subjects, the curvature of these points had negative or near to zero values, indicating that the inferobasal region had a flat appearance or was convex toward the LV cavity.

The point with the greatest curvature (i.e., angiographic apex) appeared to be shifted toward the an-


LEFT VENTRICULAR CURVATURES - DIASTOLE

LEFT VENTRICULAR CURVATURES - SYSTOLE

FIGURE 1. Regional curvatures in patients with inferior myocardial infarct (M.I.) *(closed triangles)* and in normal subjects *(open squares)*. Curvatures are reported as dimensionless values. *Vertical bars* indicate SEM. Scaling of values is 10^{-2}. *Asterisk on abscissa line* indicates level of significance probability <5% comparing data of patients with those of normal subjects.

teroapical region (normal subjects = point 46.3 ± 2.3; patients = 44.9 ± 2.8; $p < 0.05$). Diastolic and systolic lengths of the anterior and inferior hemiperimeters of both groups are reported in Table II. The length of the inferior hemiperimeter (from apex to mitral fornix) was significantly greater in patients owing to a reduction in systolic shortening.

TABLE II Length of Anterior and Inferior Hemiperimeters

	Normal Subjects	Inferior Myocardial Infarction	p Value
Diastolic AWL (mm)	303 ± 19	294 ± 31	NS
Diastolic IWL (mm)	249 ± 31	252 ± 27	NS
Systolic AWL (mm)	212 ± 25	224 ± 33	NS
Systolic IWL (mm)	192 ± 20	221 ± 27	0.0001

AWL = anterior wall length; IWL = inferior wall length; NS = not significant.

TABLE III Correlation Between Curvature and Left Ventricular Function

Curvature Point	LV Ejection Fraction	Asynergy Extension
76	−0.3243	NS
77	−0.4004	NS
78	−0.4597	0.2711
79	−0.5044	0.3181
80	−0.5445	0.3653
81	−0.5761	0.4182
82	−0.5816	0.4507
83	−0.5822	0.4935
84	−0.5177	0.4428
85	−0.4123	0.3561
86	−0.3502	0.3136

Correlation r values for curvature values, and asynergy extension and LV ejection fraction. Curvature points are numbered from aortic corner (point 1) to mitral fornix (point 90). Only significant values are represented.
LV = left ventricular; NS = not significant.

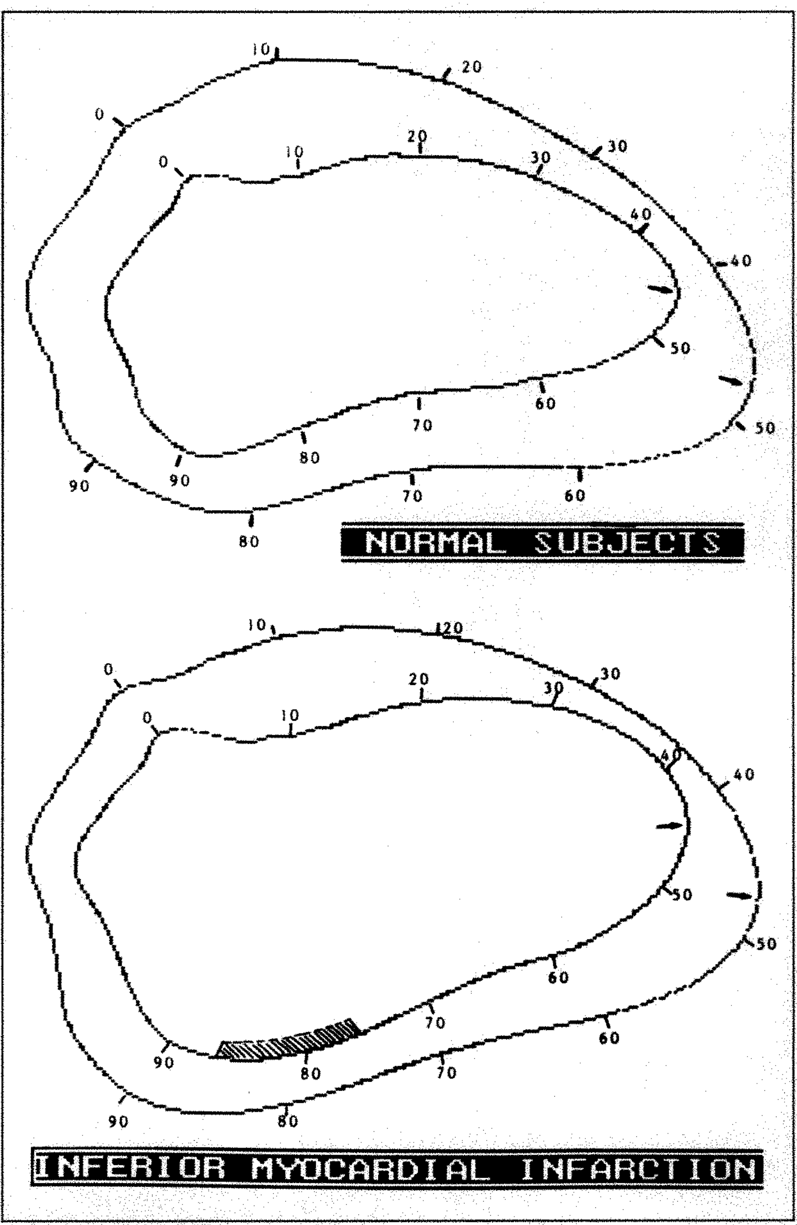


FIGURE 2. Representative mean diastolic and systolic outlines in normal subjects and patients with inferior myocardial infarct reconstructed from Fourier analysis. *Arrows* indicate apex. *Dashed zones* on inferior myocardial infarct outlines indicate regions whose curvatures are correlated to end-systolic volume index.

In patients, the systolic curvature of the inferobasal region from point 78 to 86 showed a significant direct correlation with A% and from point 76 to 86 a significant inverse correlation with LV ejection fraction (*Table III*), *indicating that the more positive the curvature values of this region, the greater the A% and the lesser the LV ejection fraction.*

Patients with healed inferior wall myocardial infarction showed an impairment of LV function comparable to that reported by previous studies.[3,6,14] The extension of wall motion abnormalities (as shown by the centerline method) was analogous to that reported by Sheehan et al.[11,15] Modifications of the LV shape in inferior myocardial infarction were mild and qualitatively not easily recognizable. Quantitative analysis of regional curvature is a new way to analyze these patients.[16] Patients with inferior wall myocardial infarction had a greater than normal systolic curvature of the anteroapical and inferobasal regions. However, the difference in parietal curvature of the anteroapical region is only illusory. The analysis compared the curvature values of couples of points beginning at point 1, located at the aortic corner, and proceeding clockwise to point 90, corresponding to the mitral fornix. Due to the greater length of the inferior hemiperimeter in the patients, the comparison was obtained between points equivalent for the number of order and not for anatomic location. When LV contours of the 2 groups were superimposed using the apex as the hallmark, the anteroapical region showed no significant difference in parietal curvature (Figure 3). Thus, the distinctive characteristics of LV shape in inferior myocardial infarction are the greater length of the inferior wall and the outward (positive) curvature of the inferobasal region in the end-systolic LV contour.

A hypothetical interpretation of the causal link between shape alterations and inferior wall damage is complex. Reduced longitudinal shortening of the inferior wall (a region where longitudinal fibers are prevalent)[17] can explain the increased length of the inferior wall at end-systole. Reduced systolic displacement of the atrioventricular plane in patients with a previous inferior infarct has been described by echocardiographic studies[18] and attributed to a reduction in longitudinal shortening of the inferior wall.

The abnormality of regional curvature in the inferior infarct mainly consisted of a rounding of the inferobasal wall that had a positive curvature at end-systole, indicating a concavity of LV contour toward the cavity. This shape alteration showed a significant correlation to the extent of segmental wall damage (expressed by A%) and to the reduction in global ejection fraction. In normal subjects, the end-systolic curvature of this region usually has near to zero or negative values. Because the left ventricle has almost circular short-axis sections, the inferior wall normally has a catenoid shape at end-systole. Given that the intraventricular pressure is still increased at end-systole, the negative curvature of the inferior wall indicates a strong tangential tension opposing the radial stress, which would give a spheroid shape to the left ventricle. If this hypothesis is correct, the prevailing dam-

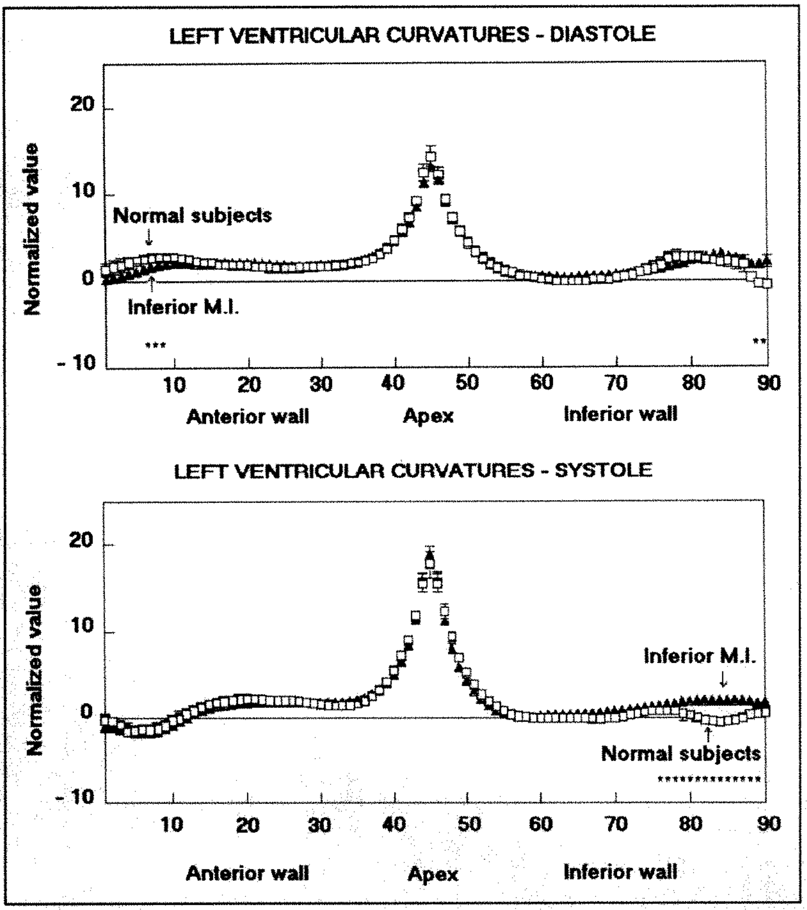


FIGURE 3. Regional curvatures in patients with inferior myocardial infarct (M.I.) *(closed triangles)* and in normal subjects *(open squares)*. Curvatures are reported as dimensionless values. *Vertical bars* indicate SEM. Scaling of values is 10^{-2}. *Asterisk on abscissa line* indicates level of significance probability <5% comparing data of patients with those of normal subjects. Mean ± SE data of 2 groups were computed using apex as hallmark.

age of longitudinal fibers would account for the reduced apex-to-base shortening and for the outward end-systolic curvature of the inferobasal wall in inferior myocardial infarction.

The minor degree of wall motion alterations that has been observed in the inferior compared with the anterior infarct (even when the extent of anatomic lesion is the same) can be explained by considering the limitations of the methods frequently used to evaluate segmental wall motion. Most methods evaluate the movement of endocardium toward the ventricular cavity, overlooking the longitudinal component of inferior wall asynergy.

As in previous studies,[1-3] our results indicate that wall expansion is infrequent in the inferior infarct. The diastolic length of the inferior hemiperimeter was not significantly different from that of normal subjects. A higher parietal stress due to the greater curvature radius of the anterolateral wall has been considered a factor leading to wall expansion in anterior myocardial infarction, with eventual development of anterior aneurysm.[5,7] The catenoid shape of the inferior wall at end-systole, lowering parietal stresses,[19] may exert a protective action against wall stretching and thinning.

In conclusion, the inferior wall in patients with an inferior wall myocardial infarction showed a decreased longitudinal shortening and a greater concavity than in normal subjects, which correlated with asynergy extension and pump function. The normal negative curvature of this wall may protect against aneurysm formation in this infarct location.

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Coronary Angiography with Four French Catheters

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In coronary angiography, there is a trend to use smaller catheters in order to avoid puncture site complications and minimize hospital stay.[1-4] It is a standard practice in our laboratory to perform routine coronary angiography with 6Fr catheters. Recently, 4Fr catheters have been introduced for angiography. This prospective randomized study addresses the performance of 4Fr catheters for diagnostic coronary angiography compared with 6Fr catheters.

The study population comprised 200 consecutive unselected patients (168 men, mean age 61 ± 10 years, range 31 to 82) undergoing diagnostic coronary angiography (excluding patients with pure valve disease). The angiography was performed through a femoral artery with a 4 and 6Fr sheath (puncture hole diameter 1.67 mm for 4Fr and 2.30 mm for 6Fr). In 36 patients in the 4Fr and 7 in the 6Fr group, the procedure was done without a sheath (puncture hole diameter 1.35 mm for 4Fr and 2.00 mm for 6Fr). Cordis (Cordis Europa N.V., the Netherlands) catheters and 0.035 inch (0.89 mm) guidewires were used exclusively. The internal diameter of the 4Fr catheters used was 0.040 inch (1.02 mm) and of the 6Fr 0.050 inch (1.27 mm). The patients were randomized to 4 or 6Fr catheters in the catheterization laboratory using the sealed envelope system. Procedure duration and fluoroscopy time for coronary angiography, quantity of radiographic contrast medium used, length of cine film, quality of ventriculography (1 = excellent, to 4 = bad), occurrence of streaming (incomplete opacification of arteries), ease of catheter manipulation

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TABLE I Technical Problems

	4 French (n = 100)	6 French (n = 100)	p Value
Dislodgment from ostium			
Right coronary artery	34	6	0.0001
Left coronary artery	27	4	0.0001
Streaming			
Right coronary artery	9	4	0.05
Left coronary artery	26	2	0.001

(1 = very easy, to 6 = impossible), torque control (1 = excellent, to 4 = bad), time to achieve hemostasis at puncture site, and need for different French size were analyzed. The quality of the cine film was assessed by the operator and an additional cardiologist. Nonionic contrast medium and premedication with nitroglycerin were used in all cases. Heparin (2,500 U) was given according to the physician's preference at the beginning of the procedure in 51 patients (51%) in the 4Fr group, and 56 (56%) in the 6Fr group. Statistical analysis was performed using the chi-square test and the unpaired t *test. Values are expressed as mean ± standard deviation.*

There were no cardiac or puncture site complications and no significant problem with ostial wedging in either group. Adequate angiograms were obtained in 97% of patients. In the group with 4Fr catheters, a crossover to another French size was required in 4 patients (4%) owing to difficulty in engaging the coronary ostia versus 2 patients (2%) with 6Fr catheters (difference not significant). No significant differences between 4 and 6Fr catheters (including time after crossover to another French size) were seen in total duration of the procedure (496 ± 262 vs 475 ± 383 seconds), fluoroscopy time (381 ± 224 vs 420 ± 557 seconds), quantity of contrast medium (91 ± 30 vs 97 ± 47 ml), length of cine film (75 ± 36 vs 71 ± 26 seconds), and number of catheters per patient (3.1 in both groups including the pigtail catheter for ventriculography). The quality of ventriculography was judged slightly better with 6Fr catheters (1.8 ± 0.6 vs 2.0 ± 0.8 with 4Fr, $p = 0.05$). There was a significantly higher incidence of dislodgment from the ostia with 4Fr catheters (31 vs 5%, $p = 0.0001$) (Table I). The incidence of streaming was also higher with 4Fr catheters (18 vs 3%, $p = 0.001$). The technical facility was judged to be similar in both groups. Torque control was perceived as slightly better with 4Fr catheters (1.6 ± 0.6 for right and 1.5 ± 0.6 for left coronary catheters with 4Fr vs 1.7 ± 0.8 for right and 1.7 ± 0.7 for left coronary catheters with 6Fr, $p = 0.05$). Compression time to achieve hemostasis was 310 ± 159 seconds for 4Fr (75 patients) versus 383 ± 151 seconds for 6Fr (74 patients, $p = 0.01$); the remaining 51 patients underwent immediate angioplasty and therefore were not included for the hemostasis analysis. There were no early or late puncture site complications.

The reported incidence of local vascular complications with coronary angiography is 4 to 12%.[5,6] Smaller catheters are likely to reduce these complications.[1,4] However, there are concerns about the quality of angiography and technical difficulties with smaller catheters. This study addresses these aspects concerning the recently introduced 4Fr catheters.

Adequate coronary angiograms were obtained with 4Fr catheters in 96% of patients versus 98% with 6Fr. The high incidence of dislodgment of 4Fr catheters from the coronary ostia, because of their reduced stability and the increased velocity of the exiting contrast medium, resulted in streaming, particularly in the left coronary artery. Streaming did not occur with a stable position of the 4Fr catheters, indicating that it was not a consequence of limited flow. This technical difficulty did not impact on the length of procedure, the quantity of contrast medium used, or the length of cine film. None of the procedures had to be repeated because of inadequate quality for clinical decision making.

An interesting finding was the superiority of 4Fr catheters in terms of torque control. This is explained by a novel shaft technology based on a new material "Pellethane," not yet implemented in 6Fr catheters used. The advantage of the small puncture hole with 4Fr catheters was evident from the significantly reduced time to achieve hemostasis. Moreover, 4Fr catheters can be easily introduced without the usual blade incision of the skin.

Limitations of the 4Fr catheters are the need to stint the pigtail catheter with a guidewire to pass the aortic valve and the restriction to guidewires ≤ 0.035 inch (0.89 mm). Angiography with 4Fr compared with 6Fr catheters requires more skill, particularly in preventing dislodgment from the coronary ostia during contrast medium injection, which has to be done vigorously to achieve adequate flow. They should therefore be reserved for experienced angiographers.

In conclusion, 4Fr catheters permit an adequate diagnostic coronary angiography in 96% of patients. Compared with 6Fr catheters, there is a higher incidence of catheter dislodgment leading to streaming. However, this can be corrected in most cases and does not compromise overall quality to a clinically significant degree. The smaller puncture hole reduces compression time and may ultimately allow for earlier ambulation, shorter hospital stay and reduction of puncture site complications.

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Comparison of Intravenous Dosing Regimens for Maintaining Steady-State Procainamide Levels During Programmed Ventricular Stimulation

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Intravenous procainamide hydrochloride has prognostic value for drug efficacy in electrophysiologic testing in patients with sustained ventricular tachycardia[1,2] and is often used as an initial screen for drug therapy in these patients. To evaluate the effects of varying intravenous procainamide dosing regimens on providing stable plasma concentrations of the drug in the clinical electrophysiology laboratory, we compared procainamide dosing and maintenance infusions determined by population kinetics[3] with those of a standard fixed dose and maintenance infusion.[2]

Fifteen patients received an intravenous procainamide dose calculated by population kinetics (group A) of 17 mg/kg of ideal body weight, with a maintenance infusion of 2.8 mg/kg of average body weight per 60 minutes. Fifteen patients received an intravenous procainamide dose using a standard fixed dosing regimen (group B) of 1,000 mg, with a maintenance infusion of 5 mg/min. Bolus in both groups A and B was administered at a rate of 50 mg/min. If hypotension developed (systolic blood pressure <95 mm Hg), intravenous normal saline solution was administered simultaneously with procainamide, without reduction of bolus or infusion rate.

All patients had inducible sustained ventricular tachycardia or fibrillation in the absence of antiarrhythmic medications, and procainamide was administered as an initial therapeutic antiarrhythmic drug trial. Patients were randomly assigned to group A or B. One patient in group B developed spontaneous sustained ventricular tachycardia after infusion of 600 mg of the procainamide bolus; the arrhythmia was terminated with burst pacing. This patient was excluded from analysis.

Ventricular stimulation procainamide began after an equilibrium period on maintenance infusion after completion of the intravenous procainamide bolus. An average equilibrium period of 15 to 20 minutes was established so as to not unnecessarily prolong electrophysiologic testing, and enable reasonable equilibration of the plasma procainamide concentration. Stimulation involved attempts at reinduction of ventricular tachyarrhythmia using up to 3 extrastimuli at up to 3 drive cycle lengths at up to 2 right ventricular sites.

Plasma procainamide samples were obtained immediately before beginning drug bolus, at the beginning of programmed ventricular stimulation and at the conclusion of electrophysiologic testing on procainamide; samples were obtained from a limb contralateral to that used for drug infusion in all patients. Samples were immediately labeled and centrifuged, and the plasma was frozen. Plasma and N-acetyl procainamide levels were determined by quantitative enzyme immunoassay (EMIT® QST™, SYVA Inc., Palo Alto, California).[4]

Plasma procainamide concentrations were compared within individual patients and between groups using paired and nonpaired t *tests, with statistical significance defined by $p \leq 0.05$.*

There was no significant difference between patients in groups A and B with respect to age, height, real body weight, time between completion of intravenous procainamide bolus and initiation of electrophysiologic testing on procainamide (i.e., equilibrium period), duration of electrophysiologic testing on procainamide, and total duration of electrophysiologic study (Table I).

Comparison of measured plasma and N-acetyl procainamide concentrations demonstrated no significant difference between groups A and B at the beginning or end of electrophysiologic testing. Plasma procainamide concentrations within group A decreased significantly during the electrophysiology study, whereas there was no significant change in group B. Plasma N-acetyl procainamide levels increased significantly during electrophysiologic testing in both groups A and B (Table II).

Despite no significant difference in plasma procainamide concentration between groups before or after elec-

TABLE I Patient Demographics

	Group A (n = 15)	Group B (n = 14)
Age (year)	63 ± 14	63 ± 11
Height (inches)	67 ± 5	68 ± 3
Real body weight (kg)	76 ± 14	81 ± 12
Equilibrium period (min)	18 ± 11	14 ± 4
Duration of EP on PA (min)	31 ± 22	21 ± 8
Total duration of entire EP study (min)	84 ± 45	58 ± 29

Values are represented as mean ± SD. There were no significant differences between groups.

EP = electrophysiologic testing; PA = procainamide hydrochloride.

TABLE II Mean Plasma and N-Acetyl Procainamide Hydrochloride Concentrations

	Group A	Group B
Pre-EP PA (μg/ml)	8.5 ± 2.1	8.1 ± 2.4
	p <0.016	p = NS
Post-EP PA (μg/ml)	7.6 ± 1.8	7.7 ± 2.3
Pre-EP NAPA (μg/ml)	1.0 ± 0.54	1.2 ± 0.49
	p <0.002	p <0.001
Post-EP NAPA (μg/ml)	1.3 ± 0.60	1.4 ± 0.60

Values are represented as mean ± SD.

NAPA = N-acetyl procainamide hydrochloride; NS = not significant (p >0.05); other abbreviations as in Table I.

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TABLE III Dosages of Procainamide

	Group A	Group B	p Value
Bolus (mg)	1,142 ± 224	1,000 ± 0	<0.025
Duration of bolus (min)	25 ± 4	20 ± 2	<0.002
Maintenance infusion rate (mg/min)	3.4 ± 0.7	5 ± 0	<0.001
Total PA dose (mg)	1,301 ± 277	1,280 ± 53	NS

Values are represented as mean ± SD.
Abbreviations as in Tables I and II.

trophysiologic testing, patients in group A received a significantly larger bolus of intravenous procainamide (infused over a longer period of time). The lower maintenance infusion rate in group A (calculated by population kinetics) may have contributed to the significant reduction in mean plasma procainamide concentration in group A after electrophysiologic testing compared with that before testing (i.e., at end of equilibrium period). Plasma procainamide concentrations were maintained more reliably during electrophysiologic testing in group B patients (i.e., with a 5 mg/min intravenous infusion rate). Total dosages of procainamide administered were not significantly different for the 2 groups (Table III).

We conclude that calculation of intravenous procainamide bolus and maintenance infusion dosages based on the population kinetic dosing regimen used in this study adds little to achieving or maintaining adequate plasma procainamide concentrations during programmed ventricular stimulation in the clinical electrophysiology laboratory. There appears to be a trend toward higher plasma procainamide concentrations with population kinetic bolus dosing, but this difference is not statistically significant compared with the population kinetic maintenance dosing formula used. A fixed maintenance infusion rate of 5 mg/min appears to provide greater stability of drug concentrations; this may reflect the higher infusion rate in group B (Table III). However, even at the 5 mg/min maintenance infusion, procainamide levels drifted (though not significantly) lower. This suggests that even higher maintenance infusion rates may be necessary for stability of procainamide levels if electrophysiologic testing is prolonged further.

The minor differences in drug concentrations recorded after bolus and maintenance infusion may not be clinically relevant over the duration of electrophysiologic testing examined in this study. Differences in maintenance infusion rate may have greater significance with more prolonged infusions. N-acetyl procainamide concentrations with either dosing regimen remained well below the active ("therapeutic") range.

Some variability in results may be anticipated for patients of varying body mass. The effects of alternate dosage regimens and infusion of other antiarrhythmic medications have not been studied. However, these results suggest the use of a straightforward, standardized method of intravenous procainamide administration for clinical electrophysiologic testing.

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Usefulness of Total 12-Lead QRS Voltage in Diagnosing Left Ventricular Hypertrophy in Clinically Isolated, Pure, Chronic, Severe Mitral Regurgitation

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Electrocardiographic criteria for diagnosing left ventricular (LV) hypertrophy are known to be relatively nonspecific and insensitive. Several studies from this laboratory[1-7] and elsewhere[8-10] have described total 12-lead QRS voltage in various cardiac diseases, and most have found this criterion to be more sensitive than previously described criteria. We examined total 12-lead QRS voltage in 24 necropsied patients with chronic, pure, isolated mitral regurgitation, and compared its sensitivity to the Sokolow-Lyon and Romhilt-Estes criteria for diagnosis of LV hypertrophy.

The 24 patients ranged in age from 21 to 84 years (mean 42); 13 (54%) were women and 11 (46%) were men (Table I). All 24 patients had clinical evidence of mitral regurgitation for >5 months. None had clinical or hemodynamic evidence of associated mitral stenosis, and none had evidence of aortic valve dysfunction. Additionally, all 24 patients had New York Heart Association functional class III or IV congestive heart failure, and 9 (38%) had mitral valve replacement or repair from 1 to 120 days (mean 25) before death. Cardiac catheterization was performed in 19 (79%) of the 24 patients and the recorded pressures are listed in Table I. To be included in this study, 1 or more 12-lead electrocardiograms recorded within 400 days of death (always before a mitral valve operation) had to be available for examination. The amplitude of the QRS was measured from the peak of the R wave to the nadir of either the Q wave or

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TABLE I Clinical and Hemodynamic Data in the 24 Patients with Clinically Isolated, Pure, Chronic Mitral Regurgitation

								Pressures (mm Hg)				
								LA				
Case No.	Necropsy No.	Age (yr)	Gender	Valvular Etiology	Duration of Cardiac Symptoms (yrs)	MVR	Interval MVR to Death (days)	m	v	LV (s/d)	SA (s/d)	RV (s/d)
1	A63–234	21	F	Rheumatic	11	+	2	15	30*	—	120/70	40/3
2	A56–200	23	F	Rheumatic	12	0	—	31	55*	—	125/75	60/7
3	A60–208	23	F	Rheumatic	8	0	—	30	45*	—	125/75	48/12
4	A70–221	24	M	Rheumatic	5	+	17	16	28*	90/8	100/60	30/6
5	A69–240	30	F	Rheumatic	6	+	2	30	65*	102/14	110/78	58/12
6	A60–131	30	M	Rheumatic	5	+	1	30	48	115/20	135/80	—
7	A57–150	31	F	Rheumatic	7	0	—	23	44*	—	118/74	—
8	A58–213	33	F	Rheumatic	3/4	0	—	—	—	—	115/80	—
9	A60–270	38	F	Rheumatic	9	0	—	32	60	115/15	120/70	—
10	A62–232	38	M	Rheumatic	2	+	7	20	39	108/16	120/84	48/8
11	A59–39	39	F	Rheumatic	6	0	—	30	55	125/20	150/65	35/4
12	A64–98	41	F	Rheumatic	6	+	1	—	—	106/15	106/60	34/10
13	A67–178	43	M	Rheumatic	3	0	—	16	28	148/13	150/84	43/4
14	A54–21	49	M	Rheumatic	3	0	—	26	60*	—	170/100	64/0
15	A63–24	28	M	MVP-RCT	1	0	—	—	—	—	130/80	23/5
16	312579	60	F	MVP-RCT	6	0	—	—	—	—	120/70	—
17	A69–62	65	M	MVP-RCT	3/4	+	120	—	—	—	—	—
18	226434	84	M	MVP-RCT	20	0	—	—	—	—	135/80	—
19	A56–59	41	M	MVP+RCT	2	0	—	32	39*	—	150/70	110/21
20	A70–244	56	M	MVP+RCT	7	+	28	25	40	100/12	110/65	42/6
21	A70–280	60	M	MVP+RCT	4	+	50	17	20*	118/17	120/80	110/21
22	A62–19	24	F	IE+RCT	3/4	0	—	27	66	108/11	108/85	—
23	A75–63	54	F	IE+RCT	2	0	—	—	—	110/15	120/70	50/10
24	A72–8	64	F	IE+RCT	12	0	—	38	50*	120/20	120/70	85/18
	Mean	42	—	—	6	—	25	23	43	113/14	125/75	55/9

*Pulmonary arterial wedge rather than left atrial pressures.

ECG = electrocardiogram; IE = infective endocarditis; LA = left atrium; LV = left ventricle; m = mean; MVP = mitral valve prolapse; MVR = mitral valve replacement; RCT = ruptured chordae tendineae; RV = right ventricle; SA = systemic artery; s/d = peak systole/end-diastole; v = v wave.

the S wave, whichever was deeper, according to the method of Siegel and Roberts[1] *(Figure 1). The electrocardiographic criteria used to diagnose LV hypertrophy included the Sokolow and Lyon Index*[11] *(sum of* SV_1 *plus the larger of* RV_5 *or* $RV_6 > 35$*), the Romhilt-Estes point score*[12] *(a system using ST-T-segment changes, QRS axis, left atrial abnormality, QRS duration and duration of the intrinsicoid deflection in addition to electrographic voltage criteria), and a method using a sum of the amplitudes of the QRS complexes of all 12 leads. Amplitudes were standardized to 10 mm equaling 1 mV.*

The hearts at necropsy were examined by WCR and the etiologic classification was made by him.[13] *In no patient was the mitral regurgitation the result of myocardial ischemia. Although 3 patients (nos. 13, 17 and 21, Table I) had narrowing (in each case by atherosclerotic plaque) of a single (left anterior descending in each) major epicardial coronary artery, none had LV fibrosis or necrosis as a result. Only 1 (no. 20) of the 24 patients at necropsy had a grossly visible myocardial lesion, namely necrosis; the lesion was secondary to a coronary embolus in the early postmitral valve replacement period, and the electrocardiogram analyzed was that recorded just before the mitral valve operation. Therefore, none of the 24 patients had grossly visible LV lesions when the electrocardiograms used in this study*

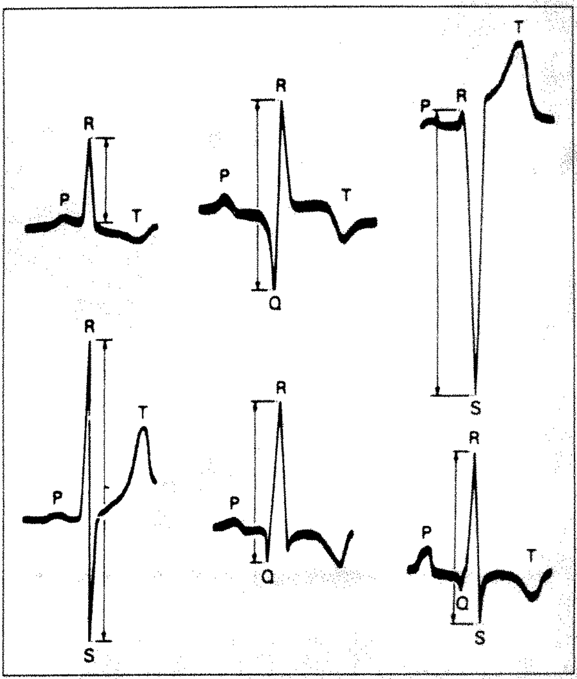

FIGURE 1. Various electrocardiographic QRS complexes showing how the voltage (in mm) was measured. (Reproduced with permission from *Am Heart J.*[1])

TABLE II Electrocardiographic Findings in the 24 Patients with Clinically Isolated, Pure, Chronic Mitral Regurgitation

Case No.	Days ECG Recorded Before Death	Chronic AF	VR (beats/min)	QRS Axis	Leads												Total QRS	R-E Score	S-L Index	S Wave V_1	R Wave V_5 or V_6	HW (g)
					I	II	III	AVR	AVL	AVF	V_1	V_2	V_3	V_4	V_5	V_6						
1	5	+	85	30	10	12	16	6	15	13	8	27	28	24	37	23	219	4	38	8	30	400
2	14	+	85	120	14	16	10	16	11	13	13	40	42	40	38	37	290	4	30	4	26	600
3	15	+	60	60	5	17	18	8	7	17	7	15	33	32	33	36	228	4	39	6	33	400
4	68	+	75	75	5	25	27	15	13	26	12	38	39	30	44	42	316	4	44	10	34	520
5	3	+	140	45	7	9	10	7	8	10	10	15	26	25	23	13	163	1	33	10	23	480
6	13	+	70	30	5	15	11	8	4	11	20	40	50	18	54	58	294	5	78	20	58	600
7	50	+	85	90	4	10	9	5	6	10	8	14	33	34	35	19	187	4	33	7	26	675
8	9	0	90	60	7	18	13	14	8	18	30	40	30	26	36	30	270	5	55	22	33	490
9	213	+	80	60	5	12	17	5	7	15	9	15	32	18	38	32	205	4	44	6	38	450
10	43	+	80	30	5	17	15	10	5	15	24	50	62	40	80	41	364	5	87	7	80	675
11	39	+	60	90	4	15	15	7	7	16	15	30	24	20	30	18	201	4	40	14	26	450
12	2	+	70	60	4	14	17	6	7	15	8	23	31	33	25	13	196	1	25	3	22	470
13	154	+	65	80	2	5	7	5	4	6	5	21	40	22	18	14	149	1	25	7	18	550
14	16	+	65	0	5	15	10	8	5	12	10	17	38	35	45	30	230	4	48	10	38	700
15	11	0	120	120	10	17	26	4	17	21	5	26	43	52	44	24	289	4	15	5	10	600
16	330	+	70	60	4	8	6	5	4	7	5	12	15	35	28	25	154	4	36	6	25	440
17	400	0	110	−45	10	8	8	7	8	9	28	38	26	23	46	48	259	9	70	22	48	640
18	50	+	75	60	5	13	8	8	4	9	12	9	11	18	18	17	111	1	29	12	17	400
19	5	+	140	110	14	25	18	16	12	20	22	20	40	50	40	33	310	3	26	4	22	775
20	30	+	90	−45	6	6	8	4	7	8	14	19	19	10	14	14	129	4	28	14	14	750
21	57	0	65	120	10	10	12	6	9	10	8	44	40	34	36	21	240	4	25	5	20	710
22	9	0	120	90	3	7	8	5	7	8	6	17	23	10	9	11	114	1	14	4	10	350
23	260	+	70	45	6	8	5	7	5	7	9	10	22	27	28	15	149	1	29	9	20	500
24	8	+	100	120	4	12	14	6	7	11	10	26	44	40	24	10	208	4	18	10	8	430
Mean	75		86		6.4	13.1	12.8	7.8	7.8	12.8	12.4	25.3	33.0	29.0	34.3	26.0	220	3.5	38	9	28	544

AF = atrial fibrillation; ECG = electrocardiogram; HW = heart weight; R–E = Romhilt-Estes; S-L = Sokolow-Lyon; VR = ventricular rate.

were recorded. The hearts of the 11 men ranged in weight from 400 to 750 g (mean 629) (normal ≤400), and those of the 13 women, 350 to 675 g (mean 472) (normal ≤350).

The electrocardiographic findings are summarized in Table II. Nineteen patients (79%) had chronic atrial fibrillation. Left atrial abnormality was present in 1 of the 5 patients in sinus rhythm. The QRS complex width was ≥0.12 second in 1 patient (no. 19, Table II), and he had a right bundle branch pattern. All 24 patients were being treated with digoxin at the time of the study electrocardiogram. The total 12-lead QRS amplitude in the 24 patients ranged from 111 to 364 mm (mean 220). (The upper limit of normal for total QRS amplitude of 175 mm was first suggested by Roberts and Day[3] and validated by Odom et al[5] who found that the upper limit yielded a specificity of 100% in subjects whose hearts weighed <400 g.) Of the criteria examined, the total 12-lead QRS amplitude had the highest sensitivity (71%) (Table III). Although the 12-lead QRS amplitude was more sensitive than the other 2 criteria examined, heart weight did not correlate with the total 12-lead QRS amplitude (Figure 2).

TABLE III Sensitivity of Electrocardiographic Criteria for Diagnosing Left Ventricular Hypertrophy in 24 Necropsy Patients with Clinically Isolated, Pure, Chronic, Severe, Mitral Regurgitation

Electrocardiographic Criteria	No. (%) of Patients Above Normal Limit
Total 12-lead QRS amplitude < 175 mm	17 (71%)
Sokolow-Lyon index (SV_1 + RV_5 or RV_6 (larger) > 35mm)	11 (46%)
Romhilt-Estes point score ≥ 5	4 (17%)

This study examined total 12-lead QRS voltage and other more standard electrocardiographic criteria for diagnosing LV hypertrophy in patients with clinically isolated, pure, chronic, severe mitral regurgitation. The highest sensitivity among the criteria for LV hypertrophy in our study group was the total 12-lead QRS voltage (71%). In these patients, the criteria of Romhilt and Estes and Sokolow-Lyon index were relatively insensitive (17 and 46%, respectively).

This study is the first to examine total 12-lead QRS voltage in patients with mitral regurgitation. Several

TABLE IV Comparison of the Sensitivity of Total QRS Voltage in Identifying Left Ventricular Hypertrophy of Various Etiologies

	Normal (n = 17)*	Aortic Stenosis (n = 50)	Aortic Regurgitation (n = 30)	Hypertrophic Cardiomyopathy (n = 57)	Idiopathic Dilated Cardiomyopathy (n = 49)	Amyloid (n = 30)	Mitral Regurgitation (n = 24)
Age (years) (mean)	41–74 (54)	16–65 (48)	19–65 (45)	14–87 (49)	19–75 (48)	21–93 (58)	21–84 (42)
Heart weight (g) (range)	288–392	380–880	375–1110	290–1230	400–940	370–900	350–900
Mean	351	606	696	593	614	532	550
Total QRS voltage (mm) (range)	84–159	144–417	109–428	66–339	74–281	58–199	111–364
Mean	124	257	270	197	153	104	220
Patients with 12-lead QRS voltage > 175 mm	0 (0%)	47 (94%)	27 (90%)	30 (53%)	20 (41%)	2 (7%)	17 (71%)

*Patients with heart weights < 400 g.

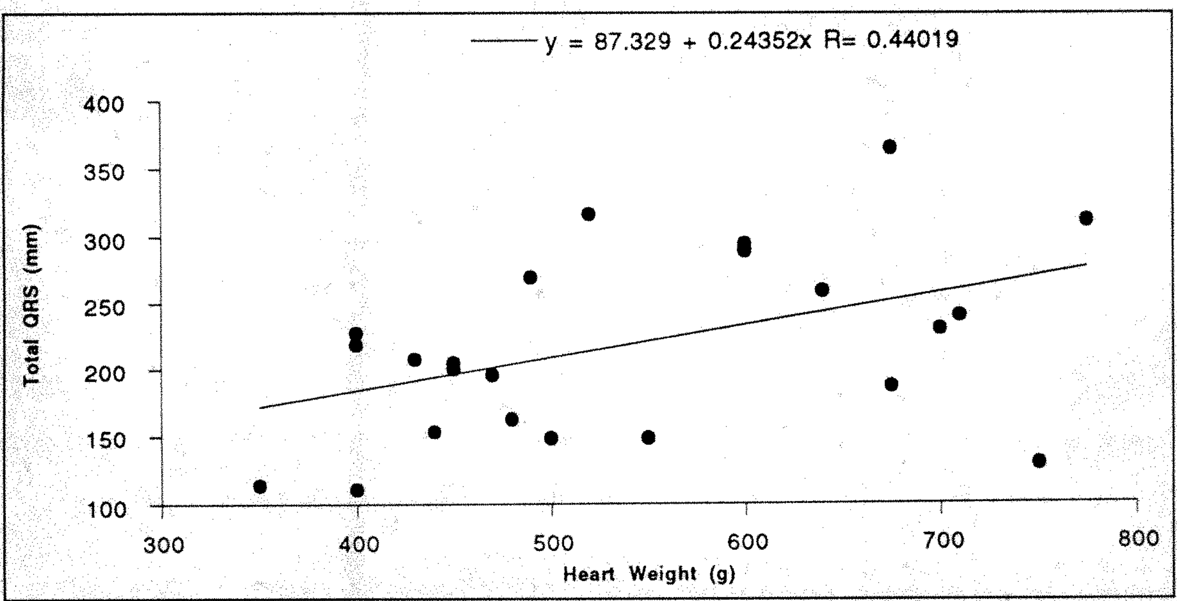

FIGURE 2. Relation between total QRS amplitude and heart weight at necropsy in 24 patients with isolated pure, chronic, severe mitral regurgitation.

studies, however, have evaluated the relation between the total 12-lead QRS voltage and heart weight at necropsy in other cardiac diseases (Table IV).[1-3,5-7]

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Postpartum Cardiomyopathy Associated with Maternal Cocaine Abuse

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The dramatic increase in the medical complications of cocaine abuse is an important health problem, and in pregnancy, maternal cocaine abuse is particularly serious. Cocaine affects both the mother's health and the developing fetus. Cocaine passes through the placenta and is metabolized slowly by the fetus. Obstetric[1,2] and fetal[1-3] complications have been reported. In addition to these documented adverse effects of cocaine abuse during pregnancy, there may be cocaine-related maternal cardiovascular complications. We report on 3 mothers who abused cocaine during pregnancy and presented postpartum in congestive heart failure due to dilated cardiomyopathy.

Case 1: A 30-year-old women (gravida 1, para 1) presented 1 month postpartum with marked pedal edema, orthopnea and dyspnea. She had a primum atrial septal defect and cleft mitral valve repaired at age 12. After repair, pulmonary artery and right ventricular pressures were normal with mild residual mitral regurgitation. She subsequently was in good health, but had a 3-year history of snorting cocaine, which continued dur-

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TABLE I Summary of Patient Characteristics

	Pt. 1	Pt. 2	Pt. 3
Age (year)	31	29	33
Cocaine abuse (year)	3	2.5	1
Route of administration	Inhalation	Intravenous	Intranasal
Dose (g)	0.2–1.25	1.0	—
Frequency during pregnancy	Daily	Every other day	Every other day
Other substance abuse	Alcohol Marijuana	Alcohol Marijuana	Heroin
Cigarette smoking	+	+	+
Previous cardiac disease	ASD, primum (repaired)	0	0
Obstetrical history	Primiparous	Multiparous	Multiparous
Preceeding delivery	Term infant	34 weeks	Term infant
Birth weight (g)	2,260	2,000	3,580
Clinical presentation	CHF	CHF, DVT	CHF
Months postpartum at onset of symptoms	1	3	1
Radionuclide ejection fraction %	19	39	NA
Echocardiogram: LVDD/LVSD (cm)	5.5/4.8	5.8/5.0	6.2/NA
Echocardiogram at 1 year: LVDD/LVSD (cm)	4.3/2.0	5.0/3.6	4.6/3.3*

*Obtained at 28 weeks of subsequent pregnancy, 17 months from initial presentation with heart failure.
ASD = atrial septal defect; CHF = congestive heart failure; DVT = deep venous thrombosis; LVDD = left ventricular diastolic dimension; LVSD = left ventricular systolic dimension; NA = information not available.

ing pregnancy. She freebased cocaine (Table I) 4 to 5 times weekly, but denied intravenous use. Also during pregnancy, she abused alcohol (1 pint weekly), smoked 1 pack of cigarettes daily and marijuana once weekly, as she had for the past 10 years. Her pregnancy was uncomplicated, but owing to her history, she underwent a cardiac evaluation and had clear lungs, a widely split second heart sound and a grade I/VI systolic flow murmur. An echocardiogram at 38 weeks gestation (Figure 1A) revealed left ventricular dimensions at the upper limits of normal, fractional shortening of 30%, mild tricuspid regurgitation and a cleft anterior mitral valve leaflet. The patient continued to abuse cocaine, alcohol and marijuana until delivery. Labor and vaginal delivery at term were uneventful, and both the baby's and mother's urine tested positive for cocaine metabolites. The patient presented 1 month postpartum with symptoms of biventricular failure and denied cocaine use. Her blood pressure was 100/60 mm Hg. Her heart rate was 120 beats/min, irregularly irregular. There was jugular venous distention 6 cm above the sternal angle. She had pulmonary rales. A third heart sound and murmur of tricuspid regurgitation were noted. Her liver was tender, pulsatile and measured 10 cm below the costal margin. She had pitting edema of the legs. An electrocardiogram demonstrated atrial fibrillation with a rapid ventricular response. An echocardiogram (Figure 1B) revealed biventricular dilatation and depressed fractional shortening of 13%. Radionuclide angiography revealed a dilated, diffusely hypokinetic left ventricle with an ejection fraction of 19%. After strict bed rest, salt restriction, digoxin, diuretic, captopril and warfarin, she improved, was discharged and advised to abstain from alcohol and cocaine. Although clinically improved, 4 months later the ejection fraction was 21%. However, 14 months after initial presentation, her ejection fraction was 44% with reduction in ventricular size. An echocardiogram (Figure 1C) revealed normal left ventricular size and fractional shortening without tricuspid regurgitation.

Case 2: A 29-year-old woman (gravida 3, para 4) with history of protein S deficiency, recurrent deep vein thrombosis, and alcohol and cocaine abuse presented 3 months postpartum with complaints of dyspnea, orthopnea and paroxysmal nocturnal dyspnea for 1 week. She had a 3-year history of cocaine and 10-year history of alcohol abuse. She had used cocaine intravenously, approximately 1 g/week during pregnancy, but postpartum admitted smoking 1 to 2 g of cocaine only on weekends. Her alcohol consumption had decreased from daily to 1 pint/week during pregnancy. She smoked marijuana and 1 pack of cigarettes daily. This pregnancy was complicated by deep venous thrombosis (as were her previous pregnancies), and she was receiving subcutaneous heparin twice daily. Preterm labor at 34 weeks was followed by an uncomplicated vaginal delivery. The patient was in moderate respiratory distress. Her blood pressure was 110/80 mm Hg, heart rate 110 beats/min and respiratory rate 28 breaths/min. There were bilateral pulmonary rales. Jugular venous distention was 12 cm above the sternal angle. She had a parasternal lift, and her point of maximal impulse was displaced laterally. There was an increased pulmonic component of the second heart sound, a third heart sound, a grade III/VI holosystolic murmur at the apex, and a grade II/VI murmur of tricuspid regurgitation. There were mild hepatic tenderness and pitting edema to the knee. An electrocardiogram demonstrated sinus tachycardia and diffuse T-wave abnormalities. An echocardiogram revealed left atrial and ventricular dilatation, a markedly reduced fractional shortening of 13%, severe mitral regurgitation, moderate tricuspid regurgitation and small posterior pericardial effusion. A radionuclide ventriculogram revealed diffuse hypokinesia with an ejection fraction of 39%. A ventilation-perfusion lung was read as intermediate probability of a pulmonary embolus, but was not confirmed by pulmonary angiography. She was treated with digoxin, diuretics and captopril, and was to enroll in a drug treatment program. An echocardiogram 10 months later revealed decrease in left ventricular size and improved fractional shortening of 28%.

Case 3: A 33-year-old woman (gravida 7, para 4) with history of intranasal cocaine and heroin abuse 4 to 5

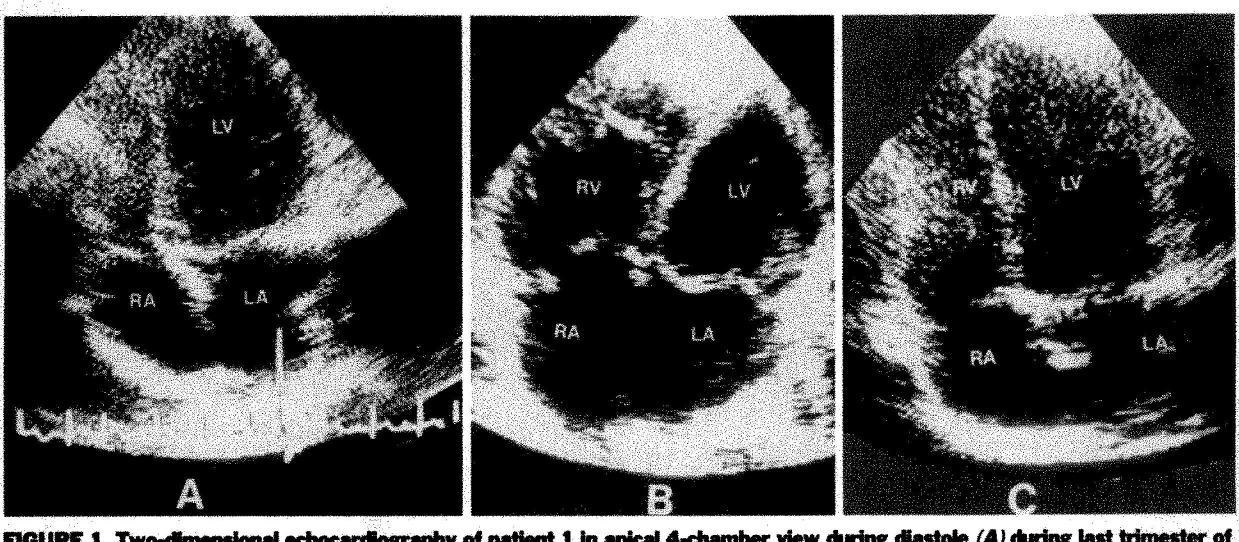

FIGURE 1. Two-dimensional echocardiography of patient 1 in apical 4-chamber view during diastole *(A)* during last trimester of pregnancy, *(B)* during hospitalization for congestive heart failure 1 month postpartum, and *(C)* 14 months postpartum. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

times weekly during pregnancy presented 1 month after vaginal delivery with complaints of 2 weeks of dyspnea, orthopnea and paroxysmal nocturnal dyspnea. Valid information about her drug abuse was not available. She had no history of cardiac disease. Her blood pressure was 130/90 mm Hg and heart rate 80 beats/min. Respiratory rate was 24 breaths/min and labored. Bibasilar pulmonary rales were present. Cardiac examination revealed a new third heart sound. Her abdomen was unremarkable, and no pedal edema was noted. A chest x-ray revealed cardiomegaly and congestion of the pulmonary vasculature. An electrocardiogram demonstrated sinus rhythm with diffusely inverted T waves. An echocardiogram revealed marked left ventricular enlargement and hypokinesia. She improved with digoxin and diuretics. She continued intranasal abuse of heroin and cocaine. She became pregnant 2 years later after discontinuing cocaine use. She continued to use heroin in the first 2 trimesters and had an uncomplicated pregnancy, labor and delivery on methadone. An echocardiogram during the subsequent pregnancy revealed normal ventricular dimensions and contractility, with a normal fractional shortening of 40%.

Maternal cocaine abuse during pregnancy was associated with cardiomyopathy occurring in the postpartum period. Given the low overall incidence of postpartum cardiomyopathy (1 to 2 cases/4,350 deliveries yearly at our institution), it is unusual that 3 women should present within 1 year. Patient characteristics, drug abuse profile and obstetric history are summarized in Table I. The clinical presentations of these patients do not fit strict diagnostic criteria for postpartum cardiomyopathy,[4] because other factors may have contributed (anemia, alcohol and cocaine abuse, and preexisting heart disease). Patient 1 had a repaired primum atrial septal defect; however, Whittemore et al[5] did not report any cases of congestive heart failure in 20 patients with repaired atrial septal defects (39 pregnancies).

During a pregnancy complicated by cocaine abuse, there may be several potential etiologies of cardiomyopathy. First, cardiomyopathy has been associated with cocaine abuse,[6] because there may be a direct toxic effect resulting in vasculitis/myocarditis.[7] Evidence of myocarditis was found in 8 of 40 patients who abused cocaine.[8] Biopsy-proved viral myocarditis has been reported in both chronic cocaine abusers,[7] and patients who develop postpartum cardiomyopathy.[9,10] Second, cardiac toxicity of cocaine may be a direct effect or be due in part to adulterants used such as local anesthetics, lidocaine and quinine, as well as stimulants (caffeine, ephedrine, phenylpropanolamine and amphetamines)[11] that may stimulate endogenous catecholamine release and the central nervous system.[11,12] Third, cocaine may have a direct depressant effect on the myocardium irrespective of ischemia and a local anesthetic effect, as observed in animal studies.[13] Fourth, there are known risks of endocarditis.[14] Finally, animal data suggest cardiac toxicity of cocaine may be increased during pregnancy due to changes in α-adrenergic receptor sensitivity, cocaine detoxification and body weight.[15] Cocaine abuse and the hemodynamic challenges of pregnancy may have predisposed these mothers to the development of a cardiomyopathy postpartum. Although other factors may have had a role, the association of cocaine with postpartum cardiomyopathy should be recognized and further studied.

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Left Ventricular Doppler Inflow Signals in Children with Isolated Ventricular Septal Defect

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Doppler-derived atrioventricular valve inflow indexes are used as indicators of diastolic cardiac function and were validated previously by angiocardiographic and radionuclide techniques.[1,2] In this study, mitral valve Doppler signals were examined in children with left-to-right shunting ventricular septal defects (VSD) and compared with those in normal control subjects.

Twenty children (aged 2 weeks to 15 years, mean 2.9 ± 3.9 years) with isolated VSD were studied prospectively. In 10 patients, the VSD was perimembranous and nonrestrictive. Seven patients had perimembranous, restrictive VSD. Two patients had multiple, nonrestrictive VSD, and in 1 the VSD was midmuscular. The patient cohort was separated into 2 groups according to presence (group A) or absence (group B) of clinical congestive heart failure. All 12 patients in group A were receiving digoxin at the time of the study. The control group comprised 10 age-matched, normal children.

Ten patients in group A underwent cardiac catheterization. Echocardiographic data were obtained 1 to 2 hours before cardiac catheterization. No patient had aortic stenosis or regurgitation, coarctation of the aorta, structural mitral valve abnormalities or regurgitation, patent foramen ovale, atrial septal defect, right-to-left shunting, cardiac arrhythmias, systemic hypertension or anemia. After a complete 2-dimensional echocardiographic examination with Acuson XP and 3 or 5 MHz transducers, a pulsed Doppler interrogation of the mitral valve was completed placing the sample volume at the tips of the mitral valve leaflets and parallel to the flow axis. An average of 5 consecutive cardiac cycles were obtained. Each cycle was indexed for the heart rate by dividing by the square root of the RR interval. Peak filling rate was calculated as the ratio of peak E velocity to the velocity time integral (VTI) of E and A.[2] Left ventricular (LV) end-diastolic volume and ejection fraction were calculated using biplane Simpson's formula. Dimensions of the left atrium were measured from the parasternal long-axis view at the level of the coaptation points of the aortic valve leaflets. Mitral valve annulus diameter measurements were averaged from the apical 4-chamber and parasternal long-axis views. Mitral valve area was calculated assuming the orifice to be a circle.[3] All measurements were indexed for the body surface area of each child and reported as mean ± 1 SD. Unpaired t *test was used for statistical analysis, with $p < 0.05$ indicating a significant difference.*

In group A, peak E velocity was increased significantly; however, the E/A ratio was decreased because of the significantly increased peak A velocity (Table I). In this group, LV filling rate was shifted to late diastole. This was manifested by the decreased early diastolic

TABLE I Doppler and Two-Dimensional Echocardiographic Variables

	Congestive Heart Failure				
	Pts. With (n = 12)	p Value	Pts. Without (n = 8)	p Value	Control Subjects (n = 10)
Age (year)	3.1 ± 4.7	NS	3.9 ± 2.1	NS	2.3 ± 2.2
Heart rate	113 ± 17	NS	106 ± 16	NS	114 ± 15
Ejection fraction	53 ± 6	NS	53 ± 6	NS	56 ± 6
Left atrial dimension	55 ± 16	<0.001	26 ± 3	NS	27 ± 7
Left ventricular end-diastolic volume	99 ± 51	<0.01	70 ± 18	<0.01	47 ± 10
Mitral valve area	6 ± 1	<0.01	5.0 ± 0.6	NS	5.0 ± 0.7
Deceleration time	51 ± 11	<0.005	42.0 ± 4.8	NS	39.0 ± 6.5
Pressure halftime	1.86 ± 0.60	<0.05	1.50 ± 0.17	NS	1.47 ± 0.20
Peak filling rate*	27 ± 7	<0.05	33 ± 5	NS	32 ± 7
VTI*	8 ± 3	<0.05	6 ± 1	NS	5.4 ± 1.0
Peak E*	5.0 ± 0.8	<0.005	4.0 ± 0.9	NS	4.0 ± 0.6
Peak A*	4.0 ± 0.8	<0.001	3.0 ± 0.6	NS	2.8 ± 0.6
E/A ratio*	5.0 ± 0.6	<0.001	7.5 ± 3.0	NS	6.0 ± 1.7
E VTI†	5 ± 2	NS	4.3 ± 0.9	NS	3.7 ± 0.5
A VTI†	3.3 ± 0.9	<0.001	1.5 ± 0.4	<0.005	2.1 ± 0.7
E VTI/VTI†	26 ± 2	<0.001	26 ± 10	NS	30 ± 3
A VTI/VTI†	19 ± 4	<0.05	12 ± 4	<0.05	16 ± 3
1/3 VTI/VTI†	15 ± 3	<0.01	16 ± 6	NS	18 ± 6

*×100; †×1,000 of actual values.
Values are mean ± 1 SD.
NS = not significant; VTI = velocity time integral.

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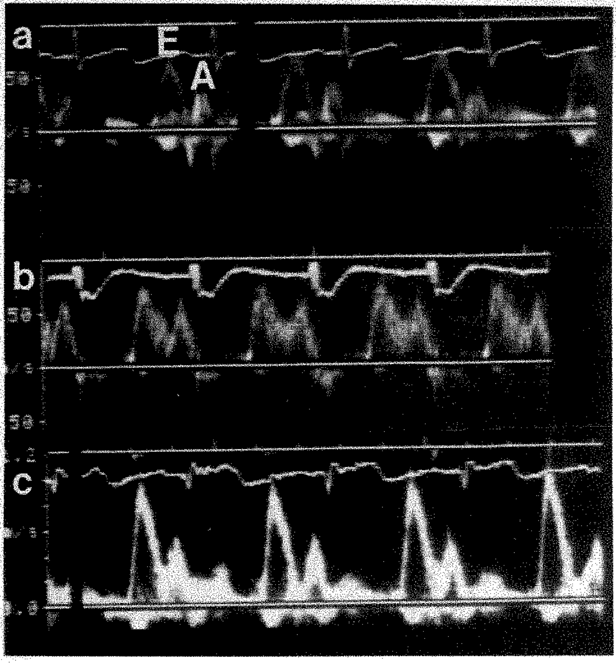

FIGURE 1. *a*, mitral valve Doppler signals of patient with ventricular septal defect and without congestive heart failure. Peak A velocity indexed for heart rate is 0.018 m/s, E/A ratio is 2, and pressure halftime is 1.5 ms. *b*, patient with ventricular septal defect and congestive heart failure. Peak A velocity indexed for heart rate is 0.043 m/s, E/A ratio is 1.2, and pressure halftime is 2.7 ms. *c*, normal subject. Peak A velocity indexed for heart rate is 0.027 m/s, E/A ratio is 1.4, and pressure halftime is 1.4 ms.

filling rate normalized for mitral stroke volume, decreased ⅓ VTI/VTI (ratio between ⅓ of velocity time integral and total time integral) and E VTI/VTI, and increased A VTI and A VTI/VTI ratio. In group B, A VTI and A VTI/VTI ratio were significantly decreased, suggesting that ventricular filling occurred primarily in early diastole. Left atrial dimension was increased only in group A. LV end-diastolic volumes were significantly increased in both groups, but more pronounced in group A. Hemodynamic data of the 10 patients in group A revealed Q_p/Q_s ratios ranging from 2.2:1 to 5.4:1 (mean 3.6 ± 1.4), ventricular end-diastolic pressures of 7.75 ± 3.6 mm Hg, and mean left atrial pressures of 10.3 ± 2.9 mm Hg. No patient had any evidence of mitral stenosis.

Earlier hemodynamic studies showed that volume-overloaded ventricles need a larger pressure increment per volume increment in late diastole than do normal ventricles.[4] Recent hemodynamic and Doppler echocardiographic combined studies showed that altered Doppler inflow signals could be seen in patients with impaired LV relaxation.[5] Limitations of diastolic function evaluation by Doppler indexes include interobserver variations and changing loading conditions of the left ventricle in the same subject. Echocardiographic studies were performed by the same investigator and within 1 to 2 hours of the cardiac catheterization to minimize the effects of these factors. Measurements were obtained by an investigator blinded to the study.

The pattern observed in group A (Figure 1) occurred in the presence of normal or slightly increased left atrial pressures. Assuming that left atrial pressure did not vary at the time of mitral valve opening, a slower rate of LV pressure reduction would result in a relatively delayed mitral valve opening prolonging the isovolumic relaxation time.[5] This would result in a decrease in peak early flow velocities. In group A, the presence of longer deceleration times may reflect a prolonged reduction in LV pressure associated with impaired relaxation, and decreased early and increased late diastolic filling rates (Table I). Doppler signals of asymptomatic patients (group B) suggest the preservation of diastolic function despite significantly increased end-diastolic volumes.

We conclude that diastolic dysfunction of the left ventricle is present in hemodynamically significant left-to-right shunting VSD with normal left atrial and LV end-diastolic pressures.

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Electrocardiographic and Echocardiographic Features of Left Atrial Size After Orthotopic Cardiac Transplantation

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After orthotopic cardiac transplantation right bundle branch block (partial or complete) and left atrial (LA) enlargement (Figure 1) are often recognized electrocardiographically.[1,2] Previously, a relation between electrocardiographic changes of LA enlargement and echocardiographic measurements of LA size has been established in the patient without cardiac transplantation.[3,4] The structural significance of finding LA enlargement on a standard 12-lead electrocardiogram after cardiac transplantation has not been previously investigated, and forms the basis for the present study.

Twenty-nine patients who underwent orthotopic cardiac transplantation at the Alfred Hospital form the

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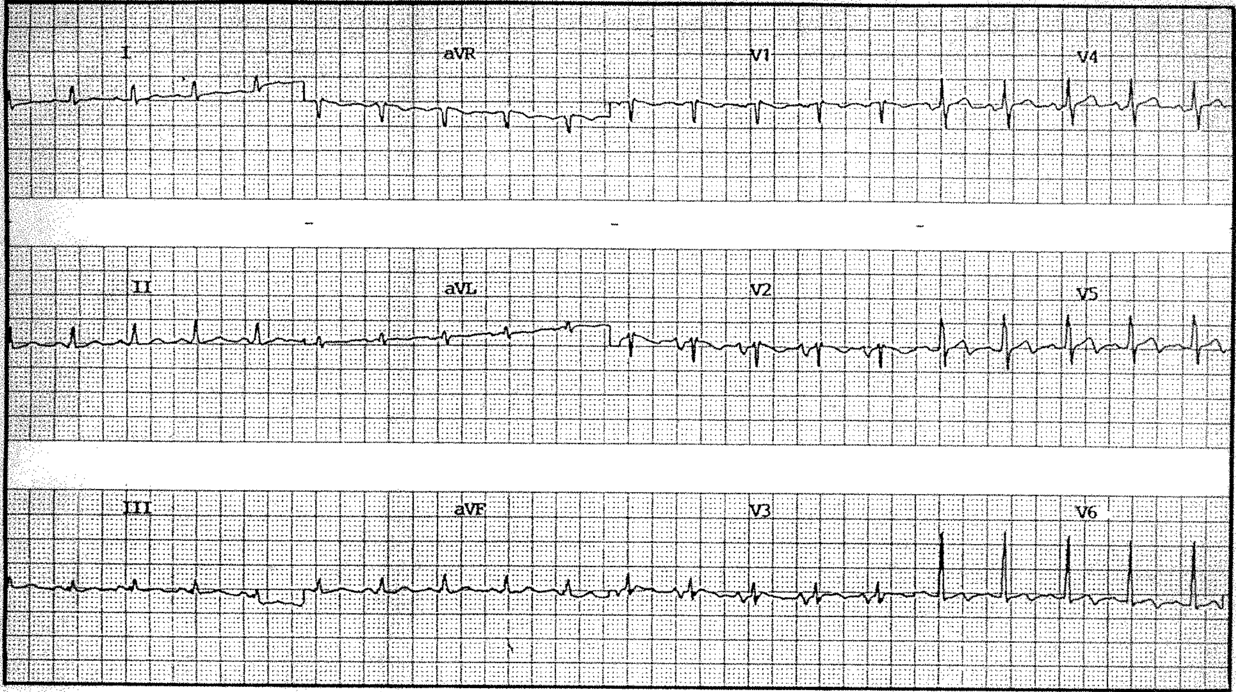

FIGURE 1. Electrocardiogram demonstrating pattern of left atrial enlargement in lead V_2 without changes in V_1.

study group. There were 26 men and 3 women (mean age 47 years, range 20 to 65). The indications for cardiac transplantation were dilated cardiomyopathy (52%), coronary artery disease (38%), valvular heart disease (7%) and acute myocarditis (3%).

Electrocardiograms were routinely performed during postoperative convalescence and at the time of follow-up examinations or endomyocardial biopsies. For inclusion in the study, electrocardiograms must have been performed during sinus rhythm and be of adequate technical quality to allow the assessment of donor P-wave morphology.

The electrocardiograms were analyzed for the presence of LA enlargement using the diagnostic criteria: P-wave duration >110 ms in lead II; negative P-wave component amplitude in lead $V_1 \geq 0.1$ mV or negative P-wave component duration in V_1 >40 ms according to Munuswamy et al.[3] In addition the P terminal force, as described by Morris et al[5] was calculated. The same electrocardiographic analysis of P-wave morphology used for lead V_1 was also applied to lead V_2 because of the observation that the P wave in V_2 was often biphasic after orthotopic heart transplantation.

Transthoracic 2-dimensional echocardiographic examinations were performed with a Hewlett Packard 77020A phased-array scanner, using either a 2.5 or 3.5 MHz transducer. Continuous electrocardiographic monitoring was performed throughout each procedure. Apical images were recorded in 2 orthogonal planes, the 2- and 4-chamber views according to the American Society of Echocardiography Standards.[6] For inclusion in the study, adequate LA imaging was required to allow accurate identification of the atrial border and the donor recipient suture line. The LA outline was planimetered to calculate maximal length and area. Measurements were performed at the time of maximal atrial dimension or at the end of the T wave.[7] After identification of the donor recipient anastomoses (Figure 2), the LA dimension was measured at this level. The maximal dimension and area of the donor left atrium were also measured in both echocardiographic planes. The total LA volume and donor LA volume were determined using the biplane area-length method.[8] All electrocardiograms and echocardiograms were obtained within 1 week of each other, and were recorded an average of 6 weeks (range 1 to 20 weeks) after surgery.

Data are expressed as mean ± standard error of the mean. Where a single patient had >1 data set available for analysis, the echocardiographic and electrocardiographic parameters were averaged. Group data were

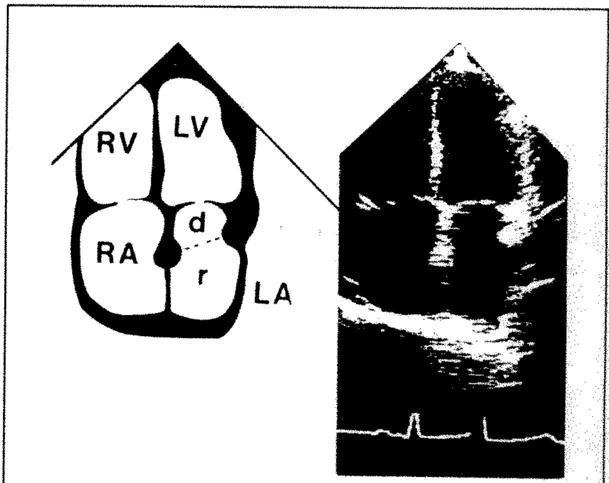

FIGURE 2. Four-chamber apical view of the transplanted heart showing suture line with divisions into donor (d) and recipient (r) components. LV = left ventricle; RA = right atrium; RV = right ventricle.

TABLE I Comparison of Indexes of Left Atrial Size According to the Presence of Left Atrial Enlargement Electrocardiographically

Echo. Parameters	Lead V_1			Lead V_2		
	LAE−	LAE+	p Value	LAE−	LAE+	p Value
Total LA						
Dimension (cm)	7.1 ± 0.1	8.3 ± 0.7	0.04	7.0 ± 0.2	7.3 ± 0.2	0.04
Area (cm^2)	26.7 ± 0.9	34.6 ± 4.4	0.04	25.7 ± 1.2	28.5 ± 1.4	NS
Volume (cm^3)	87.0 ± 4.7	122.0 ± 22.5	0.07	79.8 ± 5.2	97.0 ± 7.2	0.07
Suture line dimension	4.3 ± 0.3	4.5 ± 0.1	NS	3.9 ± 0.1	4.6 ± 0.5	NS
Donor LA						
Dimension (cm)	4.3 ± 0.1	4.5 ± 0.2	NS	4.3 ± 0.1	4.4 ± 0.1	NS
Area (cm^2)	10.7 ± 0.3	11.9 ± 0.4	NS	10.3 ± 0.3	11.1 ± 0.4	NS
Volume (cm^3)	22.6 ± 1.0	27.6 ± 0.2	NS	20.7 ± 1.2	24.7 ± 1.6	0.05

Echo. = echocardiographic; LA = left atrial; LAE− = features of left atrial enlargement, absent; LAE+ = features of left atrial enlargement, present; NS = not significant.

compared using analysis of variance, with a correction for heterogeneous variances where appropriate.

The 29 patients studied underwent echocardiographic examination on a total of 64 occasions. The indications for echocardiography were: routine assessment of allograft function (52%), deteriorating cardiac function of uncertain cause (26%), possible pericardial tamponade/effusion (10%), assessment of cardiac murmur (10%), and evaluation for a possible cardiac source of emboli (4%). Eleven of the 64 echocardiographic studies were rejected because of inadequate technical quality and 3 were rejected because they were not performed during sinus rhythm.

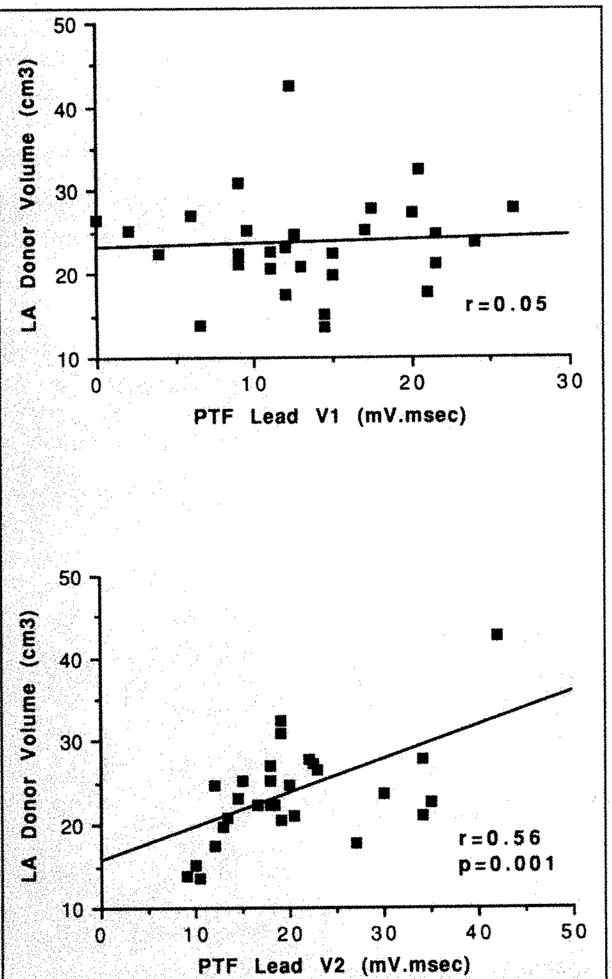

FIGURE 3. Correlation between the P terminal force (PTF) in leads V_1 and V_2 with the volume of left atrial (LA) donor component determined echocardiographically.

According to electrocardiographic criteria, there were no instances in which LA enlargement could be demonstrated in lead II. Analysis of lead V_1 revealed LA enlargement in 10% of cases and 44% in lead V_2.

Echocardiographic assessment of LA dimensions showed the following: total LA maximal dimension 7.2 ± 0.2 cm, total LA area 27 ± 1 cm^2 and total LA volume 94 ± 5 cm^3. The LA diameter at the level of the suture line was 4.3 ± 0.3 cm. Analysis of donor LA dimensions identified a maximal dimension of 4.3 ± 0.1 cm, area 11 ± 1 cm^2 and a volume of 23 ± 1 cm^3. In subjects in whom LA enlargement was present in lead V_1 total LA maximal dimension, area and volume (Table I) were significantly greater. When LA enlargement was seen in V_2 the donor LA volume was significantly greater ($p < 0.05$). A significant correlation between the donor LA volume and the P terminal force in lead V_2 (Figure 3) was also demonstrated ($p = 0.001$). No relation between the P terminal force in lead V_1 and atrial dimension could be demonstrated.

We have documented electrocardiographic features of LA enlargement in 10% of patients in whom lead V_1 was analyzed and in 44% in lead V_2. Sandhu et al[1] found LA enlargement in 107 of 242 patients (61%) who had undergone orthotopic cardiac transplantation when discharge electrocardiograms were reviewed.

At cardiac transplantation the combination of the donor and recipient atria results in atrial chambers generally larger than normal. Stevenson et al[9] compared patients who had undergone orthotopic cardiac transplantation with control subjects and found a significantly greater total LA area: 23 ± 6 versus 13 ± 3 cm^2, respectively. In addition to increasing atrial dimensions, the transplant procedure may result in posterior rotation of the heart about its long axis. This positional change relates to the anastomosis of a large proportion of the donor right atrium to the residual posterolateral component of the recipient's right atrium.[10] As a result a large right atrium is formed, which in combination with a relatively elongated ascending aorta produces long-axis rotation. Thus, the presence of P-wave morphology consistent with LA enlargement in both leads V_1 and V_2 probably relates in part to rotational effects previously described. Our study suggests that analysis of P-wave morphology in lead V_2 is a marker of relative donor LA enlargement.

Electrocardiographic evidence of LA enlargement after orthotopic cardiac transplantation occurs frequently and can be demonstrated echocardiographically to be consistent with the presence of a relatively larger left atrium. In addition, the finding of LA enlargement in lead V_2 reflects the presence of a larger donor component of the left atrium.

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